Sex Dimorphisms in Ischemic Stroke: From Experimental Studies to Clinic

Ming Jiang†, Cheng Ma†, Haiying Li, Haitao Shen, Xiang Li, Qing Sun* and Gang Chen*

Brain and Nerve Research Laboratory, Department of Neurosurgery, The First Affiliated Hospital of Soochow University, Suzhou, China

Sex dimorphisms are important factors that influence the outcomes after ischemic stroke, which include basic health status, cerebrovascular anatomy, hormone levels, and unique factors such as pregnancy and menopause. It is widely recognized that male and female respond differently to stroke. Women aged 45–74 years old showed a lower risk of stroke incidence compared to age-matched men. This kind of protection is lost with aging. Hence, there is increasing requirement to get a more comprehensive understanding of sex-based factors to stroke on stroke incidence, symptoms, and treatments. This review focuses on sex-specific mechanisms in response to stroke based on experimental studies and highlights recent findings in clinical studies including sex-differential evaluation and outcomes of stroke. Sex-based personalized medicine should be promising in stroke therapies.

Keywords: sex differences, stroke, hormone, mechanism, clinic, evaluation, tPA

INTRODUCTION

Stroke is a leading cause of death and disability worldwide. It is the fifth and fourth leading cause of mortality in men and women (1, 2). A large proportion of stroke survivors suffer from permanent disability and mood disorders (2, 3), bringing a massive burden to the society. Generally, stroke can be classified into two types: hemorrhagic stroke and ischemic stroke. Ischemic stroke is more common than hemorrhagic stroke, which accounts for 87% of stroke. Ischemic stroke is caused by clot formation in the vessels or the narrowing of vessels, which blocks or reduces cerebral blood flow. It is known that males and females respond differently to stroke. Young female mice are protected from ischemic brain injury compared to young male mice. Such resistance to ischemia in young female mice diminished in middle-aged or aged mice (4, 5). Controversies exist within the field as to whether sex differences in stroke are solely hormone dependent or involving additional mechanisms. Indeed, hormone-independent, such as genomic factors, cerebrovascular anatomy, and physical activities are thought to contribute to sex-specific differences in stroke pathology (6).

Sex-specific factors have a similar impact on women and men patients in the clinic. It has been reported that, compared to women, men show an increasing risk of stroke incidence, both at younger ages. Women aged 45–74 years have lower stroke mortality compared with age-matched men, and this advantage declines and even reverses with aging (4, 7). When it comes to stroke prevalence, there is almost no difference between women and men. However, because women often experience a longer lifetime than men, generally there are more women stroke patients than male stroke patients (8). There are almost two- to threefold more women stroke patients than men over the age of 85 years, depending on geography and race (9). As to the stroke outcomes, women are likely to have poorer stroke recovery and suffer from disability and mood disorder, resulting in a lower life quality (10). These discrepancies may result from stroke that...
usually occurs in older ages in women, when they are at a poor overall health condition (7). Based on these findings, there are tremendous sex differences in stroke incidence, prevalence, outcomes, as well as sex-dependent/independent mechanisms after experimental stroke. It indicates that the full understanding of sex dimorphisms in stroke will help clinical stroke evaluation and personalized treatment.

SEX DIMORPHISMS IN EXPERIMENTAL STROKE

Many experimental models were developed to mimic ischemic stroke in rodents. The transient or permanent middle cerebral artery occlusion (MCAO) model is one of the best animal models to study cerebral ischemia due to its high efficiency and stability as well as good quality control. A large variety of in vivo experimental stroke studies have demonstrated that, under the same MCAO condition, young female animals present minor brain infarct in the acute phase of ischemic stroke, and decreased neurological deficits in the long-term recovery period after stroke (4, 6, 11–13). This advantage of female animals is age-relied. Aged female mice did not show resistance to ischemic stroke anymore and even got more severe stroke injury, compared to male mice with the same age (4).

HORMONE-DEPENDENT MECHANISMS OF SEX DIMORPHISMS AFTER EXPERIMENTAL STROKE

Sex steroid hormones (such as estrogen, progesterone, and testosterone) are the most common explanation for sex discrepancies after stroke. These hormones, particularly estrogen, influence the physiological [such as cerebrovascular flexibility, cerebral blood flow, and blood–brain barrier (BBB) function], and pathological (such as atherosclerosis) status of cerebral circulation system. This hypothesis is supported by robust sex discrepancies observed in ischemic stroke animal models. Premenopausal female mice exhibit smaller cerebral ischemic injury than age-matched male mice, while ovariectomized female mice with the same age show comparable infarct volumes as male mice. Ovariectomized female mice given estrogen replacement get an infarct volume similar to that of intact female mice (14, 15). Large amount of evidence proved that estrogen, especially 17β-estradiol (E2), is protective against ischemic stroke in premenopausal female mice (16). Estrogen has very robust effects on endothelial cells and smooth muscle cells that promote vascular dilation and cerebral blood flow (17), while testosterone (predominate male hormone) triggers the expression of genes that enhance inflammatory response, blood–brain barrier damage, and apoptosis, and induce cell death (18). Specific receptors expressed on vascular endothelial cells and smooth muscle cells are activated by estrogen and trigger a series of downstream effects (17). Through these effects, estrogen influences cerebral vascular reactivity by (1) promoting endothelia nitric oxide synthesis and subsequent NO produce, (2) triggering vasodilation by prostanoids (such as PG12), (3) and modulate endothelium-derived hyperpolarizing factor (EDHF) activity (17).

HORMONE-INDEPENDENT MECHANISMS OF SEX DIMORPHISMS AFTER EXPERIMENTAL STROKE

It is increasingly recognized that there are hormone-independent mechanisms of sex differences. Genomic factors may play a role in the sex-based differences in stroke. It has already been reported that sex-specific gene expression, which are related to post-stroke immune regulation, inflammatory response, and cell death, may contribute to discrepancies between male and female (19). In addition, genes on the Y chromosome are partially involved in the high BP and HTM observed in male (20).

The vascular anatomy is also different between male and female. Female often have smaller arteries and heart than male, partially due to a smaller body weight. The large body size results in the enlargement of the left atrium, which is in correlation with higher stroke risk (21).

The immune system also contributes to the sex disparities by sex-differential immune cell response to ischemic stroke (Table 1). For example, an elevated immune response in female was triggered to antigenic challenge compared to male, resulting in a more efficient clearance of debris (28). In addition, inflammatory immune cells released by spleen after ischemic stroke was elevated in male mice, and the removal of spleen promotes the stroke outcomes (29–31). Females present an increase in number and function of microglia, macrophages, monocytes, and dendritic cells compared to males (25, 32). Antigen-presenting cells from females show a stronger function of presenting peptides than the same cell group in males (33). It is clear that ischemic stroke is not a single-system insult. It initiates the damage in central nervous system and interacts with the peripheral immune system (34). Microglia, astrocytes, and mast cells are activated after ischemia occurs and produce cytokines and chemokines that cause the BBB

| Cell type       | Sex-specific differences                                                                 | References |
|-----------------|----------------------------------------------------------------------------------------|------------|
| Microglia       | Female microglia exhibit a protective phenotype while male microglia exhibit an inflammatory phenotype | (22)       |
| Macrophage      | Female macrophage secrete higher level of IL-1β and IL-6                                | (23)       |
| Dendritic cells | Dendritic cells promote female predominant Th2 cytokine production                      | (24)       |
| Monocytes       | Female mice show an increasing number of monocytes compared to male                     | (25)       |
| Regulatory T cells | Regulatory T cell in female may selective up-regulated                                           | (26)       |
| NK cells        | Female have more NK cells than male                                                      | (27)       |
| Neutrophils     | Little evidence was found in subject of sex differences                                  |            |
| B cells         | Little evidence was found in subject of sex differences                                  |            |

TABLE 1 | Sex differences in immune cells after stroke.
permeability and trigger the inflammatory cells to migrate into the brain, including neutrophils, macrophages, monocytes, and other immune cells. These cells release cytokines, nitric oxide, metalloproteinases, free radicals, and other inflammatory factors that harm the central nervous system. There is an increasing expression of inflammatory cytokines (TNF-α, IL-1β, and IL-6) and chemokines (CCL5, CXCL10, and CXCL2/macrophage inflammatory protein-2) detected in the ischemic area after 6 h of experimental stroke. At the same time, enhanced secretion levels of inflammatory factors TNF-α, IFN-γ, IL-6, CCL2, and IL-2 are observed in activated peripheral immune cells (35). Inflammatory response plays an important role in the acute phase of stroke. Some easy-to-obtain inflammatory biomarkers have been proved to be useful in predicting the stroke outcome. For example, the measurement of C-reactive protein (CRP) has been recommended to evaluate the risk in ischemic patients (36). In addition, the neutrophil-to-lymphocyte ratio (NLR) has also been used as an common parameter to estimate the inflammatory response (37), which is proved to be accurate in predicting the outcomes of ischemic stroke (38) and intracerebral hemorrhage (39). Matrix metalloproteinases (MMPs) are a superfamily of endopeptidases that are able to degrade the components of the extracellular matrix. They are elevated in the inflammatory response to the BBB after ischemia stroke (40) and hemorrhage stroke (41). These biomarkers can be useful tools to assess the inflammatory level and predict the stroke outcome.

**SEX DIMORPHISMS IN CLINICAL STROKE**

**Sex Dimorphyisms in Stroke Incidence**

Men show a higher stroke incidence than women between the ages of 45 and 74 years. The incidence rates of men and woman start to be the same and women have more stroke incidence when advancing age (7, 42–44). Women older than 75 years old exhibit higher incidence rates compared to same-aged men (45, 46). Stroke risk in women increases in younger women aged 30–49 years, and a trend of the patients, especially these elderly patients, will influence the evaluation of stroke severity. Similar findings were seen in a large Chinese study that included ischemic stroke patients above the age of 75 years (58).

Most studies were carried out with neurological deficits/stroke severity as unadjusted baseline characteristics. In these studies, no sex difference in stroke severity has been reported (59, 60), although others documented increased severity in women patients (61). In summary, it seems that most sex disparities in stroke severity are explained by differences in baseline factors. Women are more likely to be disabled, independent, or institutionalized before the stroke (56, 62), even after age adjustment (63). Future studies should include not only age and sex-specific differences in risk factors but also factors such as living status and pre-stroke function in their analysis.

**SEX DIMORPHISMS IN TPA TREATMENT**

Tissue plasminogen activator (tPA) is the only drug approved by FDA in treating acute ischemic stroke. A meta-analysis of 16 administrative and clinical studies reported that women are less likely than men to receive tPA treatment (OR 0.70; 95% CI, 0.55–0.88) when acute ischemic stroke occurs, although there is significant heterogeneity among these studies (64). A study of 383,318 acute ischemic stroke patients found that women with stroke symptoms onset within 2 h were about 10% less likely than men to receive tPA treatment (OR: 0.91; 95% CI: 0.86–0.95), after potential confounders adjustments (65). Moreover, data of the Nationwide Inpatient Sample from 2004 to 2010 showed that women are less likely than men to receive tPA treatment at either primary stroke centers (OR: 0.87; 95% CI: 0.81–0.94) or non-primary stroke centers (OR: 0.88; 95% CI: 0.82–0.94), after
TABLE 2 | Effect of tPA treatment on stroke outcomes and mortality.

| Patients number | Sex-specific outcomes                  | References |
|-----------------|----------------------------------------|------------|
| 2,178           | Women benefit more from tPA compared with men (p = 0.04) at 90 days | (69)       |
| 1,272           | Reduced mortality in women (p = 0.023) and improved Barthel score | (70)       |
| 887             | Women had a better outcome in the age group 51–60 years old compared with men (OR: 0.38; 95% CI: 0.15–0.96). In the age group >80 years old, men had a better outcome than women (OR: 2.69; 95% CI: 1.21–5.96). | (71)       |
| 25,777          | No difference between sexes in functional outcome (OR: 1.03; 95% CI: [0.97–1.09]; p = 0.39), males had higher risk of mortality (OR: 1.19; 95% CI: [1.10–1.29]; p = 0.00003). | (67)       |
| 9,914           | No sex difference in outcome at 3 months (adjusted OR for women: 1.41; 95% CI: [0.76–2.60]); and in 90-days mortality (adjusted OR: 1.38; 95% CI: [0.59–3.19]). | (72)       |
| 1,110           | No difference in NIHSS score and mortality between men and women | (73)       |
| 156             | At day 90, no significant sex difference in functional outcome (50.9% of women compared with 57.0% of men, p = 0.5), favorable functional outcome (61.4% of women compared with 68.8% of men, p = 0.38) | (74)       |
| 1,391           | No effect of sex was seen on outcome (OR: 1.04; CI: [0.76–1.43]); or mortality (OR: 1.13; CI: [0.73–1.73]). | (75)       |

Potential confounder adjustments (66). These sex differences in time of tPA administration are significant, because there is convincing evidence suggesting that women benefited more from tPA treatment than men (67). It is still not known why the sex disparities in tPA use exist. Women, especially elderly women, are more likely to live alone, which may lead to delayed stroke symptom recognition, emergency arrival, and tPA administration. A study of 10,048 Canadian patients with acute ischemic or hemorrhagic stroke reported that women are more likely to live alone than men (61.5 vs. 38.5%), and delayed hospital arrival within 2.5 h of onset of symptoms (OR: 0.54; 95% CI: 0.48–0.60) and receiving tPA (OR: 0.52; 95% CI: 0.43–0.63), with age and other potential confounders adjusted (68). Despite the differences in receiving tPA treatment, analysis of thrombolytic trials found that women may benefit from tPA treatment than men (Table 2).

SEX DIMORPHISMS IN ENDOVASCULAR THERAPY

According to the ischemic stroke guidelines (2015) from the American Heart Association and American Stroke Association, endovascular therapies have more advantages as treatment for acute ischemic stroke that is caused by large vessel occlusion (76). Therefore, before we go directly into the sex-based differences in endovascular treatments, the prevalence of large vessel occlusions in men and women needs to be assessed. However, these parts of data are limited. A study that collected the consecutive CT angiograms of stroke patients that arrived at the hospital within 24 h found that women are more likely to have large vessel occlusion compared to men (77). Meanwhile, a study from SITS-ISTR (Safe Implementation of Thrombolysis in Stroke International Stroke Thrombolysis Registry) showed similar results, in that there are more women stroke patients with large vessel occlusion (78). In a large study that analyzed 1.11 million hospitalized cases in Germany from 2013 to 2017, women of all ages were treated more often with endovascular therapies (OR: 1.26; 95% CI: 1.22–1.30) (79). In contrast, another study in USA that analyzed the data from the Nationwide Inpatient Sample from 1997 to 2006 showed that women stroke patients are less likely to receive endovascular therapies than men (OR: 1.73, 95% CI: 1.49–2.01) (80).

The most important predictor of outcomes of endovascular therapies is recanalization (81). However, there are few of data investigating the outcomes of recanalization or endovascular therapy. In a meta-analysis of seven randomized controlled trials on endovascular treatment within the HERMES collaboration, 1,762 patients were included and 833 (47%) are women. Functional outcome (modified Rankin Scale score, 0–2) was evaluated at 90 days. The effect of endovascular treatment and functional recovery showed no difference between men (adjusted common odds ratio [acOR]: 2.16; 95% CI: 1.59–2.96) and women (acOR: 2.13; 95% CI: 1.47–3.07) (82).

DISCUSSION

This review discusses the sex discrepancies from experimental stroke to clinical stroke. Experimental studies reveal that young intact females are protected against ischemic stroke. Both hormone-dependent mechanisms and hormone-independent mechanisms are involved. Ovariectomized female mice and intact male mice have worse stroke outcomes than intact female, while the resistance to ischemia of young females disappears with aging. The pattern is quite similar when it comes to clinical stroke. Men exhibit higher risk of stroke incidence than women between the ages of 45 and 74 years, while this kind of advantage is lost in women above 75 years old and stroke incident risks increase to the level of men or even higher. Additionally, with the great change of lifestyle in the last several decades, obesity and other metabolic associated diseases are becoming more and more common, increasing stroke incidence. This phenomenon should trigger our attention. System strategies to prevent stroke should be made to educate people with a healthy lifestyle. Although there is no obvious sex difference in stroke symptoms, stroke recognition is different between men and women. Women seem to pay less attention to acute stroke symptoms and were more likely to wait to see if the symptoms would resolve, which would miss the time window for thrombolysis therapies. The good news is, with the advance of 5G mobile network technology, stroke patients or patients with stroke mimics would have a chance to communicate to doctors immediately. Together with big data technology, pre-hospital
emergency system will be improved and it will be possible to trace the past medical history of individual patients and help doctors make personalized sex-based treatment strategies. The prediction of stroke outcomes using a clinical scoring system may be helpful for stroke treatment decision. Several outcome prediction scores were reported recently. In the study that compared two outcome prediction scores [Five Simple Variables (FSV) score and the PLAN (Preadmission comorbidities, Level of consciousness, Age, and focal Neurologic deficit)]. After following up with 575 hospitalized stroke patients at 6 months for functional status, they found that FSV score was superior to the PLAN score in predicting good outcomes [alive and live independently, modified Rankin score (mRS) 0–2], while PLAN score is better in predicting devastating outcomes (dead or live dependently, mRS 5–6) (83). With the development of AI, machine learning technologies are more and more widely used in clinical medicine because of their accuracy. A recent study investigated the application of machine learning technologies in the prediction of long-term stroke outcomes. Three machine learning models were developed, and their predictability was compared. To assess the accuracy of these machine learning models, they were compared with the Acute Stroke Registry and Analysis of Lausanne (ASTRAL) score. After evaluating 2,604 acute ischemic patients, they found that the machine learning models can improve outcome prediction in ischemic stroke patients and the accuracy of these machine learning models did not show any difference from the ASTRAL score (84). However, there is no neurological score system used to predict stroke outcomes that takes sex factor into consideration, as well as the criterion of intravenous treatments or endovascular therapies. Therefore, sex-based neurological scoring systems should be developed and sex should be considered as a factor in stroke assessments.

**AUTHOR CONTRIBUTIONS**

MJ and CM were responsible for writing the manuscript. HL, HS, and XL were responsible for its drafting. QS and GC was responsible for its revision. All authors read and approved the final manuscript.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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