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Update on specificities of stroke in women

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Summary

The majority of strokes occur in women who in crude numbers have poorer outcome including higher mortality from stroke than men. This may, however, to a large degree be explained by the preponderance of women in the older age groups. Nevertheless, incidence of stroke is higher in men than in women. Overall rates of stroke decline, but more in men than in women; consequently the excess number of strokes in women will be on the rise in the years to come.
Risk factors differ between men and women: e.g. rates of atrial fibrillation and hypertension are higher in women with stroke, while rates of e.g. smoking or high alcohol consumption are higher in men, while some risk factors including diabetes or smoking carries a higher risk in women than in men. Especially older women are less well represented in many trials, which reduces the generalizability of results to this from a stroke perspective extremely important population, however, in areas of treatment where sufficient data is available, e.g. i.v. thrombolysis or mechanical thrombectomy the benefit is equal between sexes and may even be higher in women due to their longer life expectancy. Access to care varies between regions depending both on cultural factors and the overall access to care; in especially lower income countries though data is very scarce the impression is that women's access to care is restricted in comparison to men. Specific female risk factors including pregnancy or sex hormone therapy are rare causes of stroke especially in high-income countries, however these stroke events occur early in life and have massive effect of individual families. Evidence on stroke care in these events is extremely limited and more data, also including prospective generalizable observational data is urgently needed to guide clinicians. Further more specific data on women and stroke is needed to identify if gender in some instances should guide treatment and care.

Until recently, focus on specificities of stroke in women has been limited to issues in relation to pregnancy, post-partum period, oral anticonception and hormone replacement therapy. However, there is increasing evidence that gender differences in stroke are not restricted to reproductive issues but may be of a more general nature. Overall, women suffer more stroke events than men and are less likely to recover; women account for 60 % of all stroke events.

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Gender differences have been reported in epidemiology, in distribution of risk factors, in stroke subtypes as well as in treatment benefit and in outcome. Further, trials are often imbalanced as to sex leaving especially older women highly underrepresented, reducing the generalizability to this group. This is highly problematic due to the high prevalence of stroke in older women. These differences are no doubt to some degree caused by socio-psychological factors, e.g. higher frequency of smoking in men or larger burden of post-stroke depression in women but there is also increasing evidence of influence of biological factors, including effects of sex hormones on the vasculature. Stroke in women related to reproduction remains an issue of major societal importance due to the young age of the victims and the effects on their families.

This review aims at providing an overview of gender issues in stroke with focus on women. The perspective is mainly clinical, though there is little evidence if and when investigation and treatment should differ depending on the patients' sex and on how to deal with stroke in pregnancy.

Possible biological mechanisms: oestrogens, progestreron and stroke

Sex hormones, including progesterone, oestrogens, and testosterone, influence vessel physiology, including vascular reactivity, CBF, blood-brain barrier, and atherosclerosis [1]. Oestrogen and progesterone have dilatory effects on blood vessels and increase blood flow, whereas testosterone has the opposite effect.

The vascular reactivity is affected by oestrogen by at least three mechanisms: increased production of NO, induction of vasodilatory prostanoids, and by manipulation of endothelium derived hyperpolarization factor (EDHF). NO levels are higher in females, which affects CBF and autoregulation. NO can be induced by oestrogen in animal models with ovariectomized rats [2] where oestrogen also induces a shift towards more dilatory prostanoids [3]. EDHF has a compensatory role in NO deficiency leading to vasodilatation [4]. It has been hypothesised that this shift towards a vasodilatory state leads to better perfusion and smaller final infarct sized in pre-menopausal women.

Further, oestrogen as well as progesterone reduces formation of atherosclerotic plaques by mechanisms also involving effects on smooth muscle cells and anti-inflammatory effects [5,6]. Consequently, oestrogen has been considered as a possible treatment in prevention of vascular disease in post-menopausal women; however, post-menopausal hormone replacement therapy has not shown any protection against stroke. This is also the case in recently reported trials with early initiation of therapy.

Most preclinical models are based on male rodents, also in stroke models, and no reliable model of menopause has so far been established [7]. This may theoretically reduce generalizability to females in general and more specifically because steroid hormones affect vessel wall dynamics.

Epidemiology

Incidence and prevalence of stroke in men and women

In a global perspective based on Global Burden of Disease data, stroke is reported more frequently in men in comparison to women [8]. Based on 2013 data, ischemic stroke incidence was 132.77 per 100,000 in men vs. 98.85 in women; hemorrhagic stroke incidence was 64.89 in men versus 45.48 in women [8]. Stroke incidence is lower in women in the middle-aged and older – approximately 60 % – and higher in the oldest group with a cut-off at 57–85 years [9–11] in comparison to men.

Based on US data, the prevalence of stroke can be estimated at 2.5 % in women and 2.7 % in men [12], this observed difference is markedly smaller than the 41 % higher prevalence in men reported in a global systematic review [13]; this may both come down to demographic differences and insufficient data especially in women from low-income countries. Due to the longer life expectancy in women especially in developed countries, stroke ultimately affects more women than men. When correcting the US data [12] for the preponderance of women at older age, a total of 3.1 million female stroke survivors versus 2.7 male stroke survivors can be estimated.

A decline in stroke incidence has been observed during the last 50 years in high-income country population-based studies; this decline is more marked in men than in women (30.3 % in men vs. 17.8 % in women) [14]. However, a recent worldwide review of stroke incidence, prevalence and mortality in women documented that the development in stroke epidemiology is significantly related to regions' transition in industrialization and economy. In less developed regions, data was limited due to lack of reliable registries and possibly reduced access to care and treatment for women. In especially Eastern Europe, the burden of stroke in women was on the rise, while in high-income countries, a decrease was observed [15].

Overall, more women than men are admitted with stroke in spite of higher incidence rates in men, due to the longer life expectancy in women. In low-income countries, data is limited, especially in women, while a tendency to increasing levels is observed e.g. in Eastern Europe. In high-income countries, rates are declining in both men and women, but more in men than in women, so even higher numbers of women will be admitted with stroke or living with sequels from stroke in the years to come.

Characteristics of women with stroke: age and risk factors of stroke

Women admitted with stroke are overall older and frailer than men and tend to have accumulated more risk factors at the time of first stroke [13,16]. Reported mean age in men and women