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EDITORIAL

Estrogen in ischaemic stroke: the debate continues

See paper by Pappa *et al.*, on page 1300.

Sex differences abound in the epidemiological literature on ischaemic stroke. Women enjoy a lower stroke incidence throughout most of the life span; however, this benefit dissipates with aging [1]. Women aged over 80 have higher mortality and poorer functional outcomes compared with age-matched men after stroke. Over the next 20 years, this disparity is expected to increase, and women will bear the brunt of stroke-related death and disability. Much of the 'female-protected' phenotype has been attributed to lifelong exposure to estrogen, and the rise in stroke incidence occurs concomitantly with loss of ovarian function. Because a low-estrogenic state (menopause) is associated with this transition into a higher stroke risk, the link between estrogen and stroke has been an area of interest for many stroke investigators (reviewed recently in [2]). It is now well recognized that estradiol plays a vital role in the ischaemic brain. Animal models of experimental stroke have shown that estrogen (17-β estradiol) is a robust neuroprotective agent in both men and women [3].

Despite the strong experimental evidence of estrogen's beneficial effects in pre-clinical stroke models, estrogen supplementation in clinical trials involving post-menopausal women have not been successful. In the Women's Health Initiative (WHI), administration of conjugated equine estrogen (0.625 mg/day) to post-menopausal women without a history of stroke increased stroke incidence [4]. In the Women's Estrogen For Stroke Trial (WEST) 1 mg/day of 17-β estradiol surprisingly increased mortality and morbidity in post-menopausal women with a recent TIA or non-disabling stroke [5]. Although as noted by many, numerous issues make these trials somewhat difficult to interpret such as the initiation of therapy well after menopause, use in patients with established vascular disease, and administration of supraphysiological doses of estrogen. This has led to a reassessment of the efficacy of exogenous estrogen for the prevention of stroke in post-menopausal women. However, much less is known regarding estrogen effects in the acute injury period. In this issue of The European Journal of Neurology, Pappa and colleagues evaluated serum levels of endogenous estradiol in post-menopausal women with acute ischaemic or hemorrhagic stroke [6].

In this study, serum levels of estradiol were evaluated in 302 post-menopausal women (age 73.6 ± 12.9 years; approximately 26.7 ± 10.6 years post-menopause) admitted with acute ischaemic stroke. Patients on steroid or hormone replacement therapy or women with transient ischaemic attack or subarachnoid hemorrhage were excluded. This is a novel approach as these women were evaluated in the acute period, in which data are sorely lacking. Historically, most clinical studies have focused on the effects of chronic exogenous administration of estrogen on stroke incidence. The main question addressed was whether the levels of endogenous estradiol in elderly women after stroke were associated with changes in stroke severity or outcome. The authors utilized the National Institute of Health Stroke Scale (NIHSS) and modified Rankin Scale (mRS) at both admission and 1 month post-stroke. Estradiol levels, measured acutely post-stroke, were significantly higher in non-survivors as compared to survivors 1 month after stroke. They also found that endogenous estradiol levels were an independent predictor of stroke severity as quantified by NIHSS at the time of admission. In a multivariate analysis, estradiol levels continued to be a significant independent predictor of adverse functional outcomes and handicap (mRS $\geq$ 4) 1-month post-stroke even after removing confounders such as age and initial NIHSS. As hemorrhagic and ischaemic stroke pathophysiology may differ, the authors also removed the 13% of patients with hemorrhage, repeated the analysis (261 patients), and found similar results. Importantly, as testosterone can be peripherally converted to estrogen via the actions of aromatase in adipose tissue, the authors also measured BMIs and found no association between BMI and outcomes. These findings are consistent with recent reports showing increased mortality [7] and stroke risk (also associated with greater central adiposity) [8] in post-menopausal women with higher estrogen levels.

The findings of this study suggest that high levels of endogenous estradiol are deleterious in acute stroke. The authors suggest that the concept of estrogen as a neuroprotective agent 'should be challenged'. However, these results should be interpreted with caution, and certainly these results do not definitively answer the question of whether acute estrogen is detrimental or beneficial, as well noted by the authors. There is a clear association between estradiol levels and stroke outcomes, but this does not imply causation. The

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poorer outcomes seen in women with the highest levels estradiol levels may not be a direct biological effect but simply reflective of larger lesion sizes (infarct volumes) that were not assessed in this study. Indeed, raising endogenous estradiol levels may even reflect an endogenous protective mechanism, as has been seen in animal models in which up-regulation of aromatase occurs in the infarct area, and infarct damage worsens with loss or inhibition of aromatase in the acutely injured brain [9]. Another important limitation of this paper is that the authors do not mention the exact time points at which blood samples were collected from the patients, although the authors' previous studies (using the same cohort) state that these were collected in the morning 2–3 days after onset [10]. Biomarkers of stroke outcome are known to vary widely and can be especially sensitive to stroke acuity, post-stroke infection rates, medication use, etc., many of which were not controlled for in this initial study. Additionally, levels of other endogenous estrogens (i.e., estrone) were not assessed. Future studies examining serial samples and the utilization of an age-matched control group (for example, post-menopausal women admitted to the hospital for reasons other than stroke) may provide some clarity on levels of estradiol in stress and sickness. Overall, these results, although intriguing and a large step forward, yet again demonstrate the many uncertainties related to the role of estrogen in post-menopausal women with ischaemic stroke.

Conflict of interest

None.

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