Jack Jestus
Wake Forest University
Department of Neurological Surgery

Sex and age differences in development of cerebrovascular disease in a (mRen2)27 cardiometabolic animal model

Jack Jestus, Fatima Ryalat, Nicholas Contillo, Nathan McMullan, Stephanie Coffman, Zhidan Xiang, Diz D, and Wolfe SQ

Background: In the past 20 years, no drug therapies have successfully been translated into human use for the treatment of intracerebral hemorrhage (ICH), the most devastating stroke subset. One likely factor in this is the lack of an effective animal model of human disease and comorbidities seen in the ICH population, such as hypertension and diabetes. We evaluated the transgenic cardiometabolic rodent model, (mRen2)27, in which overexpression of Ren2 results in extreme hypertension, glucose intolerance and obesity, as an appropriate ICH model.

Methods: Sprague Dawley (SD) and (mRen2)27 rats of both sexes underwent Systolic BP measurement using tail-cuff plethysmography, and weights were obtained. They were sacrificed at 14, 32, and 52 weeks and perfused with PBS and fixed by 4% paraformaldehyde. Brains were sectioned sagittally at 5 µm. Whole-brain sections were stained using Hematoxylin & Eosin (H&E) and Van Geison (VG) collagen staining techniques to visualize the pial blood vessels. The wall-to-lumen ratios for vessels were calculated and compared using a student t-test to determine significance.

Results: There was no significant difference between the SD and mRen sections in the 14 week old male cohort (SD vs mRen, 0.30±0.08 vs 037±0.09, n=3 vs 3, P=0.051). At 32 weeks old, there was a significant difference in the wall:lumen ratio of male SD vs mRen rats (SD vs mRen, 0.30±0.11 vs 0.68±0.23, n=2 vs 2; P<0.0001), while there was no significant difference between the female SD and mRen cohort (SD vs mRen, 0.30±0.09 vs 0.37±0.09, n=2 vs 2, P=0.17). At 52 weeks, there was a significant difference between the SD and mRen rats of both male (SD vs mRen, 0.28±0.10 vs 0.49±0.07, n=2 vs 2, P<0.01) and female (SD vs mRen, 0.32±0.09 vs 0.44±0.09, n=3 vs 3, P<0.05) sexes.

Conclusion: The (mRen2)27 cardiometabolic animal model demonstrates age-related sex changes in the wall:lumen ratio of cerebral vasculature consistent with cerebrovascular disease seen in ICH patients. Males develop these vascular changes earlier than females, but both sexes in this model develop cerebral vascular changes by 1 year of age. The (mRen2)27 model appears to recapitulate human disease and sex differences, and may serve as an appropriate translational model of ICH.

Supported by a pilot grant from the Wake Forest Cardiovascular Sciences Center