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Sex differences in circulating IL-12 levels in a cardiometabolic animal model

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Intracerebral hemorrhage (ICH) is the most devastating stroke subtype, with a 40% mortality rate within 30-days. Studies suggest that interleukin 12 (IL-12), a proinflammatory cytokine, plays a key role in the secondary brain response to ICH, and this may be influenced by comorbidities such as hypertension, diabetes, and cardiometabolic disorders. However, sex differences in circulating IL-12 levels have not been well-characterized. We use a clinically relevant (mRen2)27 rat model that demonstrates overexpression of tissue renin, resulting in cardiometabolic syndrome including extreme hypertension, to investigate serum IL-12 levels in cardiometabolic disease.

Methods: Serum IL-12 was measured using ELISA (ThermoFisher Scientific) in male and female (mRen2)27 and Sprague Dawley (SD) rats at 30 or 55 weeks. Systolic BP was measured using tail-cuff plethysmography.

Results: At 30 weeks, hypertensive mRen rats had higher IL-12 (pg/mL) than SD rats in both males (825 ± 58, n=8 vs. 582 ± 90, n=6, $P < 0.05$) and females (1073 ± 47, n=7 vs. 438 ± 101, n=8, $P < 0.05$). mRen females had higher IL-12 than males despite lower systolic BP (mm Hg) (183 ± 3 vs. 195 ± 4, $P < 0.05$) and lower body weight (g) (304 ± 5, n=7 vs. 583 ± 17, n=8, $P < 0.05$). On the other hand, there was no significant sex differences in BP or IL-12 in the SD rats. In older (55 week) mRen rats, systolic BP was (168 ± 4 mm Hg, n=4 in males, and 172 ± 3, n=11 in females) and IL-12 concentration was lower by 52% in males and 46% in females as compared with 30 weeks of age. There were no sex differences in BP or IL-12 at this age.

Conclusion: mRen rats with cardiometabolic disturbances have higher circulating IL-12 than control normotensive rats, with sex differences in hypertensive but not normotensive rats. Data elucidate the importance of considering sex and age as biological variables when designing preclinical ICH studies. Further studies to investigate sex differences in local cerebral cytokines and the temporal changes in response to ICH are ongoing.

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