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Gender Differences in Pediatric Stroke: Is Elevated Testosterone a Risk Factor for Boys?

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A recent advance in the field of stroke is the understanding that it is a sexually dimorphic disease, that is, outcomes and disease mechanisms are influenced by the individual's biological sex. The overall incidence of stroke is higher in men versus women in most nations, a trend that cuts across ethnic background.¹ This sexually dimorphic epidemiology extends well beyond the menopausal years and is clearly present in young children.^{2–5} For example, stroke incidence as estimated from a state-wide hospital discharge database emphasize that boys carry higher risk for all stroke types than do girls.² Boys also have a higher case fatality rate for ischemic, but not hemorrhagic, stroke than do girls in this same report. In the International Pediatric Stroke Study, ischemic stroke is more common in boys, regardless of age, trauma history, or stroke subtype.³

There is also a suggestion that stroke outcome, like risk, is influenced by sex or sex in combination with age. In aggregate, animal studies predominately in young adult rodents have demonstrated that males sustain greater histological damage after experimental stroke than females. However, in humans and aging animals, infarction size and functional outcome after cerebral ischemia can paradoxically be worse in females than in their male counterparts (for reviews, see Hurn et al,⁶ Herson et al,⁷ Reeves et al,⁸ and Liu et al⁹). Furthermore, cellular and molecular death mechanisms are not always identical in the male versus female brain or in XX versus XY cell cultures (for a recent review, see Cheng and Hurn¹⁰). Examples of molecules that have sexually dimorphic roles in cerebral ischemic injury mechanisms include apoptosis-inducing factor, caspase 8, poly-adenosine diphosphate ribose polymerase, nitric oxide synthase, glutathione, Akt, astrocytic aromatase, glial fibrillary acidic protein, angiotensin II type 2 receptor, and the P450 enzyme, soluble epoxide hydrolase. Such studies emphasize the importance of biological sex yet do not discount the importance of gonadal sex steroids or brain-derived neurosteroids as modulators of oxidant, toxic, and ischemic challenges to the brain. The vast majority of this information has come from in vivo studies of gonadally intact or castrated adult animals with or without hormonal replacement, as well as in vitro studies that remove specimens from circulating hormones.

We know very little about these factors in pediatric stroke. In this issue of *Annals of Neurology*, Normann et al provide provocative evidence that the male child's risk for arterial ischemic stroke or cerebral sinovenous thrombosis is linked to androgen availability.¹¹ Specifically, elevated plasma levels (>90th percentile for age and gender) of the principal circulating androgen, testosterone, were found to be associated with a 4–5-fold increased risk of cerebrovascular disease after adjustment for pubertal status, cholesterol, and hematocrit.

Furthermore, among the boys, there was a dose–response relationship such that for each 1nmol/l increase in testosterone level, the odds of stroke were increased. This novel finding is the first to address androgens in pediatric stroke and is consistent with the rather sparse literature that androgens impact ischemic outcomes and mechanisms of brain damage.^{7,12–16} In contrast, low circulating testosterone levels are associated with higher stroke incidence and worse outcomes after stroke in men.^{12–16} Importantly, androgen levels dramatically drop after both experimental and clinical stroke in adults.^{14–16} In experimental studies that control pre- and postischemic androgen levels, androgens can reduce or exacerbate ischemic damage, further confusing the issue.^{16,17} In the study by Normann et al,¹¹ testosterone levels were measured in cases 6 to 12 months after the ischemic event and assumed to reflect prior circulating levels and thus risk. However, regardless of this limitation, it is clear that further clinical and experimental studies are necessary to understand the involvement of circulating androgens in pediatric stroke.

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