Commentary

Sex influences in neurological disorders: case studies and perspectives

Janine Austin Clayton, MD

Beginning in the late 1980s and early 1990s, scientists and the public alike recognized that, for too long, women had been underrepresented in clinical trials. While much progress was made in the following decades, preclinical research still often ignores sex as a fundamental biological variable. Many neurological disorders, including multiple sclerosis and migraine, show strong sex differences in incidence and disease manifestation. In this commentary, we highlight case studies of neurological disorders affecting men and women to demonstrate the need for more such studies. Research conducted in these areas so far has shed light on the underlying mechanisms of the disease and offers the promise to help develop more personalized treatments for both men and women.

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Author affiliations: Office of Research on Women's Health, National Institutes of Health, Bethesda, Maryland, USA

Address for correspondence: Office of Research on Women's Health, National Institutes of Health, 6707 Democracy Blvd., Suite 400, Bethesda, MD 20892, USA
(email: janine.clayton@nih.gov)

Progress in recent decades

The Office of Research on Women's Health at NIH was established in 1990 to promote research on women's health within and beyond NIH. Today, thanks to the NIH Revitalization Act of 1993 and changes in NIH guidelines, just over half of participants in NIH-funded clinical trials are women. However, in preclinical studies, sex continues to be largely ignored.

Starting this year, researchers applying for NIH grants have to explain how they will account for sex as a biological variable (SABV) in vertebrate animal and human studies.[1] This will benefit men and women, as rigorous research into sex differences will elucidate basic biology and develop more individualized treatments for both sexes.

Sex can potentially affect a disease process through differences in chromosomal complement, gene expression, hormones, organs, and a variety of physiologic processes (see following reviews for more information).[2-5] While this discussion is centered on sex differences, both sex and gender can exert nervous system influences in humans. The case studies below highlight examples of how sex affects neurological disease processes and underscore why more research is needed on sex and gender influences in the nervous system.

Multiple sclerosis

Multiple sclerosis (MS) is an autoimmune disease characterized by progressive degeneration of the central

nervous system (CNS). It is twice as common in women, but men tend to have a more severe and progressive form.

It can be difficult to separate the genetic effects of sex chromosomes and the effects of gonadal hormones encoded by sex chromosomes. Here, animal models can be especially useful. Researchers used an animal MS model—the experimental autoimmune encephalomyelitis (EAE) mouse—in which transgenic male mice lacked the *Sry* gene on the Y-chromosome (XY^-). Although both groups of mice were hormonally female, the female mice were still more susceptible to EAE than the XY^- mice were.[6]

More recently, researchers used bone marrow chimeras of this system to show that mice with the XY^- chromosome complement in the CNS had more degeneration in the spinal cord, cerebellum, and cerebral cortex than XX mice.[7]

Hormones also play a role, as MS relapse rates decrease in women during pregnancy but rebound higher than pre-pregnancy levels postpartum.[8,9] This clinical observation sparked investigation into the role of pregnancy hormones, likely acting through immunomodulation, in MS. Estrogen therapy is neuroprotective in the EAE mouse model.[10] The underlying neuroprotective mechanisms and targets for estrogen are being investigated as treatment options for MS in humans.

Parkinson disease

Parkinson disease (PD) is a degenerative disorder characterized by accumulation of α-synuclein and loss of dopaminergic neurons in the midbrain. Although still not fully understood, mitochondrial and lysosomal dysfunction contribute to the underlying pathology.[11] In the Western world, PD is twice as common in men as women.[12,13] Men also have earlier onset of PD, and men and women tend to experience distinct motor and nonmotor symptoms from the disease.[14-16]

Many sex-related differences have been found in animal and human studies on PD.[17-19] For example, estrogen is thought to have an anti-inflammatory effect on astroglia and to induce astroglial expression.[20,21] In a mouse PD model that uses 1-methyl-4-phenyl-1,2,3,6-tetrahydropiridine (MPTP), female mice have less severe motor symptoms than males. Following MPTP exposure, astroglial levels remain elevated much longer in the substantia nigra pars compacta—where dopaminergic neurons are depleted in PD—of female mice than that of males.[22] In contrast, the early astroglial response in male mice is thought to contribute to the injury.[23]

There are also sex differences in gene expression profiles of dopaminergic neurons.[19] Genes implicated in PD pathology, including PINK1 and α-synuclein, are upregulated in postmortem brains from control men. PD-induced changes in gene expression also show sex differences, with WNT signaling, protein kinase, and proteolysis genes upregulated in women with PD and protein and copper-binding proteins upregulated in men.[18]

Migraine

Migraine is two to three times more common in women than in men.[24,25] This difference is thought to be related to gonadal hormones, since migraine in women tends to appear around puberty, symptoms often resolve in the later stages of pregnancy,[26] and more than half of women with migraine report having menstrual-related migraines.[27]

MRI studies in men and women suffering from migraine demonstrate differences in brain structure and connectivity. Women with migraine had disease-related thickening of the posterior insular cortex, a region thought to be involved in pain perception, interoception, and emotional processing. Women with migraine also had less functional connectivity between this and other regions of the brain than did men suffering from migraine.[28] Additionally, a study using functional MRI found women with chronic migraines had more dysfunctional organization of their resting state networks than men did.[29]

Stroke

Younger men are at higher risk for stroke than women, but women's risk surpasses men's as age increases, partly because women tend to live longer.[30-32] Women also have strokes later in life and have poorer outcomes with lower quality of life.[33,34] Although women have more strokes than men do, only 38% of participants in stroke clinical trials are women,[35] and even fewer animal studies include females.[36]

Mouse ischemia models have been useful in demonstrating that men and women might respond differently to treatment following stroke. For example, the

neuronal nitric oxide inhibitor 7-nitroindozole protects male mice but increases infarction in female mice.[37] Similar results were obtained from poly-ADP ribose polymerase (PARP-1) inhibitors, indicating that different mechanisms mediate ischemic injury in men and women.[38]

The NIH Women's Health Initiative has been pivotal in revealing risk factors specific to women, finding that estrogen therapy increases the risk of stroke by 30%.[39,40] Additionally, the Women's Health Study, sponsored by NIH, showed that women suffering from migraine with aura are at two-fold greater risk for ischemic stroke than women without migraines.[41,42] The association between migraine and aura is especially strong in young or otherwise low-risk women, compared with men.[43] Studies are beginning to link brain differences seen in women with migraines to stroke, leading to insights in both fields.[44]

Epilepsy

Epilepsy is a heterogeneous condition. While the overall incidence of epilepsy is the same in both sexes, certain kinds of epilepsies and certain features of the seizures show sex differences.[45]

Temporal lobe epilepsy (TLE) is characterized by epileptic foci in the limbic system. While the higher incidence in women is debated,[46,47] men and women have distinct clinical manifestations of TLE, with women being more likely to experience auras.[48,49]

A recent study found that normal female rats showed neuronal damage in areas of the limbic system following puberty. Pilocarpine is used to model TLE in mice. When injected at high doses, it activates muscarinic receptors, leading to an imbalance in synaptic transmission and seizures. In female mice, very low doses of pilocarpine leads to neuronal loss in the limbic system. In contrast, there was no neurodegeneration in male rats.[50] While the causes or implications are unclear, this phenomenon points to a potential inherent vulnerability in females that could explain sex differences in symptoms of TLE.

Conclusion

The neurosciences field has particularly suffered from a bias toward using male animals.[36] Some researchers omit females from their research because they believe that doing otherwise would complicate an already complex field. But as these case studies highlight, animal studies can illuminate sex differences in neurological conditions and help better define how these differences affect disease progression and treatment. Failing to include female subjects has practical implications: Although women make up almost half of clinical trial participants, they continue to experience a much greater share of adverse drug reactions,[51] indicating that sex needs to be considered earlier in the process, at the animal and even cellular level. Such consideration of sex in research can help save money and lives. ❑

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