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Sex Matters: Evaluating Sex and Gender in Migraine and Headache Research

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Abstract

Significant sex differences exist in migraine and other headache disorders. Several hypotheses have been proposed to explain these differences, including fluctuations in sex hormones and receptor binding, genetic factors, differences in exposure to environmental stressors, as well as differences in response to stress and pain perception; but how valid are some of these findings and can we improve the quality of research in this field? It is notable that the preponderance of animal pain studies use male subjects to study a predominantly female disorder. Furthermore, with respect to headache and migraine sex differences, limited data have been derived from animal models. Additionally, although sex differences (based on the categorization of male vs female) may be more routinely evaluated in clinical headache research than in the basic science research, greater attention to potential differences across the life cycle of women (ie, premenopausal vs postmenopausal differences) and menstrual cycle is warranted. In this manuscript we define the differences between “sex” and “gender” and highlight the importance of their application and use in headache research. The enhanced recognition and implementation of attention to sex differences throughout the hormonal and life-cycle phase in both human and animal research will only help to strengthen and further our understanding of migraine and may help guide the direction of future headache research.

Keywords

sex; gender; headache; animal models; research; reproductive

EVALUATING SEX AND GENDER IN HEADACHE AND MIGRAINE STUDIES

Significant sex differences have been found in multiple epidemiological studies of migraine.^{1–3} Numerous manuscripts begin with some variation of the statement: “Migraine is a common and often disabling disorder that occurs in three times as many women as

men,” or “Migraine affects approximately 18% of women and 6% of men in the United States.”^{4,5}

Migraine researchers, as with general pain researchers, have begun to further define these sex-related differences. In addition to the recognition that migraine prevalence disproportionately affects women, it is now well recognized that: (1) puberty is the time women begin to demonstrate an increase in migraine prevalence as compared to men; (2) over 55% of women have menstrually related migraine; and (3) the majority of women show improvement in migraine frequency and/or severity with pregnancy and menopause.^{6–9} More recently, migraine research has begun to help expand our understanding of the mechanisms underlying these differences, and how these differences can impact therapeutic treatment choices.¹⁰

Several hypotheses have been proposed to explain these differences in migraine and other pain conditions, including fluctuations in sex hormone and receptor binding, genetic factors, differences in exposure to environmental stressors, as well as differences in response to stress and pain perception.^{11–15} Yet, in the past 10 years almost 80% of animal studies published in *Pain* included only male subjects, and only 4% were even designed to test for sex differences.¹⁶ Furthermore, even in this small percentage of studies addressing sex differences, the animal group sizes are usually not large enough to allow unequivocal inferences as to whether estrous cycle differences modify the study results or not. One consequence of this growing recognition of the preponderance of pain studies using male subjects to study a predominantly female disorder is the eloquently stated recommendation in a recent consensus report by Greenspan et al that:

... all pain researchers [should] consider testing their hypotheses in both sexes, or if restricted by practical considerations, only in females. It is invalid to assume that data obtained in male subjects will generalize to females, and the best non-human model of the modal human pain sufferer – a woman – is a female animal.¹⁰

The data on the prevalence of inclusion of female subjects in headache animal studies have not yet been examined. With the exception of the few studies specifically designed to examine sex differences in animal headache models, it is likely that the animal headache literature suffers the same paucity of female subjects as Mogil and Chanda reported in the animal pain literature.¹⁶ Furthermore, there are possibly even fewer basic headache studies which consider the effect that different menstrual or hormonal life-cycle phases may have on their results. Similarly, although sex differences based on the categorization of male vs female may be much more commonly evaluated in translational and clinical headache studies, it is likely that many have been published which draw conclusions without clearly noting the differences or the potential for differences based on when in the menstrual-cycle phase or even just simply when in the life-cycle phase, as pre- or postmenopausal, the studies were conducted.

In all phases of migraine research, awareness of such differences in sample characteristics is of importance, in order to be able to determine the generalizability of the study, and they are needed in addition to merely evaluating differences between male and female subjects. As such, the cohort age is an important factor to consider; and there is increasing awareness that those of premenopausal age (generally less than 45 years of age) should be examined separately from those of postmenopausal age (generally those older than 45–55 years).^{17–19}

The enhanced recognition of the importance of sex differences throughout the hormonal and life-cycle phase in human and animal research, and the implementation of this recognition, will only help to strengthen and further our understanding of migraine. Perhaps more

importantly, it has the potential to help to advance the therapeutic options available for the treatment of migraine and other headache disorders.

WORDS MATTER: DEFINING SEX AND GENDER

The words sex and gender are not equivalent. In Merriam-Webster's Online Dictionary the following definitions for sex and gender are found:

- **Sex:** either of the 2 major forms of individuals that occur in many species and that are distinguished, respectively, as female or male especially on the basis of their reproductive organs and structures (<http://www.merriam-webster.com/dictionary/sex>).
- **Gender:** the behavioral, cultural, or psychological traits typically associated with one sex (<http://www.merriam-webster.com/dictionary/gender>).

While sex refers to a biological difference, gender refers to a socially based phenomenon. In research, the term sex refers to a dichotomous variable (female or male), based on anatomical features such as the presence of reproductive organs or chromosomes. In contrast, gender is most appropriately viewed as continuous variable.¹⁰ Gender as a continuous variable ranges from exclusively feminine to exclusively masculine, with most individuals falling somewhere in between these extremes. Gender is what is evaluated when constructs in addition to anatomical features are considered, such as gender identity, or such as when gender roles are considered. In this light, it can be recognized that gender can influence and/or confound studies evaluating sex differences.^{10,20,21} Thus, even in human studies appropriately noted to be categorized by sex, group differences may be attributable to both sex and gender. However, most migraine and pain studies have actually classified subjects primarily, or only, based on anatomical constructs (ie, sex differences). Thus, the term “sex differences” will be used throughout this supplement, except when gender is specifically evaluated.¹⁰

The first section of the supplement will focus on the epidemiological and clinical data demonstrating and characterizing the sex-related differences in migraine. Next is a review of the genetic data that support the existence of substantial sex differences in migraine pathophysiology. This is followed by a review of the existing animal data that support the presence of sex-related differences in migraine, as well as a review of the mechanisms through which hormones may affect pain processing. Finally, the supplement ends with a review of the sex and gender-related psychosocial factors which may be of relevance to both the scientific evaluation of headache as well as the treatment.

The goal of this supplement is to summarize our current knowledge about sex and gender-related differences in migraine and headache. It is also to serve as a reminder that it is imperative that these factors are not just recognized, but also *utilized* in a meaningful manner in migraine and headache research. If we are able to accomplish this, our knowledge and the potential treatment options of this common, chronic pain disorder, which predominantly affects reproductive aged women, may be meaningfully advanced.

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