Agri 2017;29(2):51–54
doi: 10.5505/agri.2017.87369

INVITED REVIEW

Pain in women

Kadınlarda ağrı

Inna BELFER

Summary

Men and women are different in response to experimental painful stimulation, in pain attitude such as reporting pain and pain coping behavior, in symptoms and signs of painful disorders and in response to pain treatment. Both acute and chronic pain conditions have diverse prevalence among the sexes. Overall, women have more than twice higher prevalence in painful disorders compared to men. Here I review putative mechanisms underlying sex differences in pain, including genetic factors that have sex-specific or sex-biased effects controlling pain and analgesia.

Keywords: Female pain; pain; sex differences; sex-specific gene effects.

Özet

Erkekler ve kadınların deneysel ağrılı uyarılara yanıt, ağrıyı bildirme, ağrıyla başa çıkma davranışları ağrılı rahatsızlıkların semptom ve belirtileri ve ağrı tedavisine yanıt gibi ağrıya karşı tutumları farklıdır. Hem akut hem de kronik ağrılı durumların erkek ve kadınlardaki prevalansları farklılık gösterir. Genelde erkeklere göre kadınlarda ağrılı durumların prevalansı daha yüksektir. Burada, ağrının kontrolü ve yitiminde cinsiyete özgü veya cinsiyet eğilimli etkiler gösteren genetik faktörler de dahil olmak üzere ağrıda cinsiyet farklılıklarının altında yattığı varsayılan mekanizmalar gözden geçirildi.

Anahtar sözcükler: Dişi cinsiyette ağrı; ağrı; cinsiyet farklılıkları; cinsiyete özgü genetik etkiler.

When it comes to pain, the clinicians know that men and women are not the same. There are conspicuous sex differences in response to experimental painful stimulation, in pain attitude such as reporting pain and pain coping behaviors, in symptoms and signs of painful disorders and in response to pain treatment. Furthermore, the prevalence rates of both acute and chronic pain conditions differ between men and women (see Table 1). Overall, women have more than twice higher prevalence in painful disorders compared to men. Finally, male and female subjects suffer differently from pain after identical surgical procedures. A prospective trial in Austria measuring pain intensity 24 hours after surgery didn't find overall sex influence. However, when stratified for surgical procedures, the results showed that men were prone to experience a greater number of moderate pain after major vascular and orthopaedic surgery while females reported higher pain ratings after diagnostic procedures (e.g. biopsies).[1] This means that the same risk factors contribute contrarily to male and female pain.

A sex difference in pain is an understudied topic: until the 1990s, most scientific research was conducted in the middle-aged white male subjects.[2] In recent years there is raising evidence on disparities in pain perception between the sexes suggesting unique pain mechanisms and targeted analgesic strategies for women and men.

Generally, women demonstrate lower pain thresholds and higher willingness to acknowledge pain that may serve as protective mechanism. Indeed, what women are doing is recognizing a problem earlier, which gives them more of a means to deal with it; so with greater vulnerability comes greater strength.

Adjunct Professor of Human Genetics and Medicine, University of Pittsburgh, Pittsburgh, PA, USA

Correspondence: Dr. Inna Belfer. Office of Research on Women's Health, DHHS/NIH/OD/DPCPSI, Democracy II, Suite 400, 6707 Democracy Blvd, Bethesda, MD 20892-5484, USA.
Tel: +1 301-435-1573 **e-mail:** inna.belfer@nih.gov

Table 1. Sex prevalence of common pain disorders

Painful condition	Sex ratio	Painful condition	Sex ratio
Migraine headache with aura	F>M	Chronic constipation	F>M
Chronic tension headache	F>M	Pyriformis syndrome	F>M
Post-dural puncture headache	F>M	Migraine without aura	M>F
Hemicrania continua	F>M	Cluster headache	M>F
Cervicogenic headache	F>M	Post-traumatic headache	M>F
Temporomandibular joint disorder	F>M	Abdominal migraine	M>F
Fibromyalgia	F>M	Lateral femoral cutaneous neuropathy	M>F
Multiple sclerosis	F>M	Post-herpetic neuralgia	M>F
Rheumatoid arthritis	F>M	Hemophilic arthropathy	M>F
Atypical odontalgia	F>M	Ankylosing spondylitis	M>F
Burning tongue	F>M	Brachial plexus avulsion	M>F
Carotidynia	F>M	Pancreatic disease	M>F
Chronic paroxysmal hemicrania	F>M	Duodenal ulcer	M>F
Temporal arteritis	F>M	Familial Mediterranean fever	F=M
Carpal tunnel syndrome	F>M	Hereditary coproporphyria	F=M
Raynaud's disease	F>M	Acute herpes zoster	F=M
Chilblains	F>M	Burns	F=M
Causalgia	F>M	Esophageal motility disorders	F=M
Reflex sympathetic dystrophy	F>M	Chronic gastric ulcer	F=M
Hemicrania continua	F>M	Chron's disease	F=M
Chronic venous insufficiency	F>M	Neuralgia of nervus intermedius	F=M
Esophagitis	F>M	Painful ophthalmoplegia	F=M
Reflux esophagitis with peptic ulcer	F>M	Maxillary sinusitis	F=M
Slipping rib syndrome	F>M	Toothache due to dentinoenamel defects	F=M
Twelfth rib syndrome	F>M	Toothache due to pulpitis	F=M
Gallbladder disease	F>M	Cracked tooth syndrome	F=M
Interstitial cystitis	F>M	Dry socket	F=M
Acute intermittent porphyria	F>M	Vagus nerve neuralgia	F=M
Proctalgia fugax	F>M	Acute tension headach	F=M
		Clustertic syndrome	F=M

F: Female; M: Male.

Female vulnerability to pain may manifest in many areas. For somatic stimuli, females have lower sensitivity and greater ability to discriminate, higher pain ratings, and less tolerance of noxious stimuli than males.[3] For endogenous pains, women report more multiple pains in more body regions than men. Majority of chronic "functional" pain conditions such as migraine, irritable bowel syndrome, tempomandibular joint disorder and fibromyalgia predominately affect women. This vulnerability can be explained by several putative mechanisms. First of all, vaginal canal provides an additional route for internal trauma and invasion by pathological agents increasing the risk for developing hyperalgesia in multiple body regions. There are different effects of chronobiology on pain in women and men: some of them are common such as puberty and senescence or a time of day, and some are female-specific such as influences of menstrual cycle, pregnancy and menopausal changes. This is in line with reports on female prevalence in many common pain conditions increasing across the pubertal period. Sex differences in temporal patterns are likely to give rise to sex differences in how pain is "learned" and stimuli are interpreted increasing variability and wider range of pains without obvious peripheral pathology. There are sex dif-

ferences in glial cells function since glia interacts with estrogen and progesterone[4] and in serotonin /dopamine system with more prominent serotonic influences on the processing of information in males than females.[5] Finally, there are different hormonal effects on pain. A fascinating work in transsexuals of Aloisi et al. showed that gonadal hormones affect the occurrence and incidence of pain. Transsexuals who receive cross-sex hormones to develop and maintain somatic characteristics of the opposite sex may get more prone or protected depending on the hormone treatment: one-third of the male to female transsexuals developed chronic pain concomitantly with estrogen/anti-androgen treatment and showed increased pain sensitivity following hormonal therapy schedule, while about half of the female to male transsexuals treated with testosterone reported a significant improvement of the chronic pain (e.g., headache) already present before the start of treatment and had improved pain sensitivity profiles following hormonal regime.[6]

Interestingly, sex differences in pain may have genetic background. A growing body of evidence demonstrates that genes controlling severe acute or more chronic human pain have sex-specific effects. For example, gene encoding Catechol-O-methyltransferase (COMT), an enzyme that inactivates biologically-active catechols, including neurotransmitters dopamine, noradrenaline and adrenaline, modulating pain, has sexually dimorphic effects.[7] Functional polymorphic alleles in this gene affect female pain much stronger than male pain, both in animals and humans. As a result, women carrying those alleles are much more sensitive to pain compared to men and are prone to develop chronic pain conditions. A gene encoding GTP cyclohydrolase, a rate- limiting enzyme for tetrahydrobiopterin synthesis, has functional alleles protective for neuropathic pain[8] in men but predisposing women to sickle cell pain crises.[9] A gene encoding Mu-opioid receptor, a main binding site for endogenous and exogenous opioids, has a functional variant with minor allele associated with greater pressure pain thresholds and less cortical response to experimental pain in men,[10] but higher pain after cesarean section in women.[11] Moreover, a recent study in patients with low back pain and sciatica after lumbar disc herniation found that this same allele increased twice the pain intensity in women compared to men.[12] Thus, human pain genes may have sex-biased effects affecting both sexes but to different degrees; sex-specific effects affecting only one but not another sex; and sex-antagonistic effects affecting both sexes but in opposite directions.

Genetic control of sex differences in pain suggests unique molecular pain pathways in men and women. Identification of these pathways may inform clinical management of pain starting from sex-specific pain assessment to personalized pain management through sex-specific analgesia. With sex-specific pain risk signatures, the clinicians will be able to avoid expensive and/or risky treatments for those who will not likely benefit from them or recover anyway. With sex-specific analgesic response signatures, the clinicians will make informative decision on the selection of the optimal drug and dose and predict side effects of selected therapies. Finally, the recent advances in genetics and pharmacogenetics of human pain, we can expect the development of novel sex-specific pain medications and pain genetic testing specific for men and women.

Conflict-of-interest issues regarding the authorship or article: None declared.

Peer-rewiew: Externally peer-reviewed.

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