Frontiers in Neuroendocrinology 45 (2017) 18–24

Contents lists available at ScienceDirect

Frontiers in Neuroendocrinology

journal homepage: www.elsevier.com/locate/yfrne

Between mind and heart: Sex-based cognitive bias in cardiovascular disease treatment

Amanda C. Kentner [a,*], Sherry L. Grace [b,c,d]

[a] Massachusetts College of Pharmacy and Health Sciences, Health Psychology Program, Boston, MA, United States
[b] York University, School of Kinesiology and Health Science, Toronto, Ontario, Canada
[c] University Health Network, Toronto General Hospital Research Institute, Peter Munk Cardiac Centre, Toronto, Ontario, Canada
[d] University of Toronto, Faculty of Medicine, Toronto, Ontario, Canada

ARTICLE INFO

Article history:
Received 27 January 2017
Received in revised form 14 February 2017
Accepted 16 February 2017
Available online 21 February 2017

Keywords:
Sex differences
Gender disparity
Cardiovascular disease treatment
Implicit bias
Cardiovascular rehabilitation

ABSTRACT

Given that both men and women experience cardiovascular disease (CVD), a common misconception is that they have similar risk factors and clinical presentation, receive comparable treatment, and have equivalent clinical outcomes; in reality differences are observed between men and women for each of these endpoints. Moreover, these differences occur as a function of both gender and sex. A review of the literature reveals widespread bias in the selection of research subjects based on these factors, in addition to implicit patient and provider biases that impede the access of women to recommended primary and secondary CVD management. In this perspective, we identify strategies to eliminate such biases and improve women's access to CVD treatments to ensure their care is consistent with current guidelines.

1. Perspective

Recently, high profile celebrity deaths (i.e. Carrie Fisher and Debbie Reynolds) have re-ignited important social media conversations (e.g. #SexMatters4Health, #FromTheHeart, #HeartHealth) on the issue of sex and gender differences in cardiovascular disease (CVD). One common misconception of CVD is that its primary etiology, atherosclerosis, is confined to the heart. However, the clinical impact of atherosclerosis can occur anywhere throughout the blood transport or circulatory system, including the brain. Accordingly, CVD can manifest itself as myocardial infarction (MI), or stroke, among other conditions. Given that both men and women experience CVD, a second common misconception is that they have similar risk factors and clinical presentation, receive comparable treatment, and have equivalent clinical outcomes; in reality differences are observed between men and women on each of these levels. Moreover, these differences occur as a function of both sex (e.g. biological factors such as chromosomes) and gender (e.g. social/cultural factors such as roles, norms, behavior).

2. Sex differences in CVD risk factors

Traditional risk factors for CVDs include physical inactivity, poor diet (i.e., high salt, sugar, processed foods, saturated and trans fats, low intake of fruit and vegetables), tobacco exposure, abdominal obesity, hypertension and dyslipidemia (see Kentner et al., 2014). Smoking and diabetes are shown to be particularly hazardous for disease development in women when compared to men (Huxley and Woodward, 2011; reviewed in Appelman et al., 2015). In addition, it is now recognized that there are psychosocial risk factors for CVDs, such as stress, social isolation and depression (Barth et al., 2004; Rosengren et al., 2004; Leifheit-Limson et al., 2010). Women experience twice the rate of depression as men across all age groups (Pratt and Brody, 2008); this depression confers two-times greater risk of CVD onset, and two-times greater mortality in patients with CVD (Barth et al., 2004; Frasure-Smith et al., 1995; Meijer et al., 2013). Finally, there are also so-called "emerging" risk factors which are inflammatory in nature. Specifically, more recent research has established a link between polycystic ovarian syndrome (Schmidt et al., 2011), gestational diabetes (Tam et al., 2012; Carr et al., 2006), gestational hypertension and pre-eclampsia (Bellamy et al., 2007) and an increased risk of CVD. The role of hormone replacement therapy in CVD is an ongoing area of study with respect to both men and women (Spencer and Pilote, 2015).

3. The role of sex hormones in CVD pathophysiology

Observations that premenopausal women are at a reduced risk of mortality from CVD, compared to men and postmenopausal

* Corresponding author.
E-mail address: amanda.kentner@mcphs.edu (A.C. Kentner).

http://dx.doi.org/10.1016/j.yfrne.2017.02.002
0091-3022/

women, has led to the hypothesis that sex hormones may play a role in CVD risk, with ovarian hormones being protective (Mosca et al., 1997; Lisabeth and Bushnell, 2012). However, the evidence supporting this has been mixed. For example, while low endogenous levels of estradiol have been associated with increased CVD incidence (Crandall and Barrett-Connor, 2013), clinical trials demonstrate that hormone replacement therapy also elevates the risk in women (Marjoribanks et al., 2017). Moreover, arterial thrombosis risk is increased by 1.6 times in women taking oral contraceptive pills (Roach et al., 2015). Similar patterns have been reported in men with both low endogenous androgens and replacement therapy increasing CVD risk (Shores et al., 2014; Vigen et al., 2013); however more recent analyses suggest these previous studies in men were underpowered (Onasanya et al., 2016). Overall, the current state of evidence suggests that (a) the actions of exogenous versus endogenous hormones may be different, and (b) there are other mechanisms that underlie sex difference in CVD pathophysiology (i.e. sex chromosomes; see McCullough et al., 2016; Clayton and Collins, 2014).

Despite these conflicting effects on CVD risk, basic research suggests that gonadal hormones affect cardiac contractility, vasculature functioning (i.e. re-endothelialization in response to injury, remodeling), and platelet aggregation (reviewed in Mendelsohn and Karas, 2005 and Bell et al., 2013), which may underlie reported sex differences. Indeed, given that sex hormone receptors are located throughout the cardiovascular, immune, and endocrine systems, there are many pathways through which gonadal steroids may be involved in the pathogenesis of CVD. For instance, in vascular endothelial cells, estrogens increase the synthesis and activity of nitric oxide, resulting in vasodilation (Guo et al., 2005). In contrast, chronic exposure to androgens generally promotes vasoconstriction (Kienitz and Quinkler, 2008). Moreover, androgen levels have been associated with atherogenic, thrombotic, and pro-inflammatory actions (Cheng et al., 2007; Ehdaie et al., 2012; Farias et al., 2014; Wu and von Eckardstein, 2003b), and estrogens are recognized to attenuate inflammation (Gubbels Bupp, 2015); however many of these effects appear to be sex, age, cell, and in the case of replacement therapy, dose specific (Wu and von Eckardstein, 2003a,b).

4. CVD onset: sex differences in clinical presentation and bias in acute care

Men tend to experience their first MI or stroke at a significantly younger age than women (Anand et al., 2008; Appelros et al., 2009; Petrea et al., 2009), raising sex and gender differences in treatment needs and outcomes. For example, because women are often older at disease onset, they can more often be socially-isolated (i.e. retired, widowed), and are more likely to have comorbid conditions (i.e. diabetes, osteoporosis, arthritis), complicating their long-term recovery.

Although the traditional warning signs of stroke and MI are well described, awareness is not sufficient so that the public reacts in a timely fashion to facilitate treatment; an appreciation of sex differences in clinical presentation is even lower (Hemingway et al., 2008; Girijala et al., 2016). Specifically, with respect to stroke, unique symptoms in women include seizures, hiccups, mental status changes, and general weakness, among other signs (see National Stroke Association, 2017; Girijala et al., 2016; Fig. 1). In women experiencing MI, in addition to the typical clinical indicator of chest discomfort or pain, they may also (or alternatively) present with generalized anxiety, jaw or back pain, indigestion, flu-like symptoms, and/or fatigue (Canto et al., 2007; Mehta et al., 2016; Fig. 2). Notably, a survey conducted by the American Heart Association revealed that while women thought themselves to be well informed, they had difficulty identifying symptoms of ischemic heart disease. Moreover, they reported that they would be more likely to call 911 for a friend experiencing heart attack symptoms than for themselves (Mosca et al., 2013). Overall, lack of an awareness of sex differences in clinical presentation, and gender differences in self-help seeking, may have major consequences such as delayed (or lack of) testing, diagnosis, and treatment to restore blood flow (Mehta et al., 2016; National Stroke Foundation, 2017).

Recently it has become apparent that sex and gender-related factors do affect access to acute CVD care. Specifically, women tend to receive care much later in comparison to their male counterparts (D'Onofrio et al., 2015; Pelletier et al., 2014; Vaccarino et al., 2005). Upon presentation in an emergency department, it has been demonstrated that healthcare providers do not initiate the appropriate diagnostic electrocardiographs (ECGs; Pelletier et al., 2014) or reperfusion strategies (D'Onofrio et al., 2015) to eligible female patients as quickly as is the case with men, suggestive of an unconscious bias in treatment management (Spencer and Pilote, 2015). However, diagnosis of CVD may be hampered by the fact that disease is more often present in the microvasculature in women (affecting walls and inner lining of tiny coronary blood vessels; see Patel et al., 2016) compared to men who tend to have blockages in the larger and more visible coronary arteries. Ultimately however, the faster the diagnosis is made, the faster patients can be reperfused and revascularized (e.g., carotid

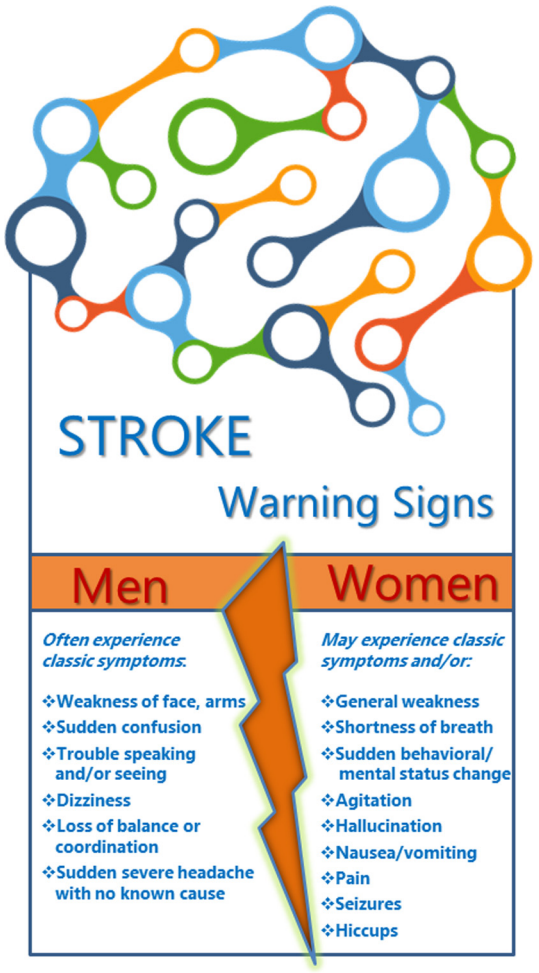

Fig. 1. Sex differences in stroke warning signs. Adapted from the National Stroke Association (2017), Girijala et al. (2016).