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What's in a name: are menopausal “hot flashes” a symptom of menopause or a manifestation of neurovascular dysregulation?

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Abstract

Hot flashes have typically been classified as “symptoms of menopause” that should be tolerated or treated until they resolve. However, mounting evidence points to hot flashes as a manifestation of one or several underlying pathophysiological processes. Associations exist between the presence, timing of onset, severity, and duration of hot flashes and the risk of several neurological (affecting sleep, mood, and cognition) and cardiovascular conditions. In addition, four consistent patterns of vasomotor disturbances have been identified across different countries, making it unlikely that these patterns are solely explained by socioeconomic or cultural factors. The changing hormonal environment of menopause may unmask differences in the autonomic neurovascular control mechanisms that put an individual woman at risk for chronic conditions of aging. These differences may have a genetic basis or may be acquired across the life span and are consistent with the variability of the clinical manifestations of aging observed in women following bilateral oophorectomy. It is time to investigate the pathophysiological mechanisms underlying the four patterns of vasomotor symptoms more closely, and to shift from describing hot flashes as symptoms to be tolerated to manifestations of an underlying autonomic neurovascular dysregulation that need to be addressed.

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Keywords

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“What's in a name? that which we call a rose; by any other name would smell as sweet.” (William Shakespeare, *Romeo and Juliet*, lines 43-44, Act-II, Scene-II) In this well-known phrase, Juliet stresses that the importance of a person (or a thing) derives from what it is, not from what it is called. However, although names are just labels, they often carry unconscious meaning and bias that can diminish the worth or detract from the attention that the thing may deserve. Take for example, vasomotor symptoms, the “hot flashes” (“hot flushes”) and night sweats that women may experience as they transition to menopause and thereafter. These “flashes” and “sweats” have typically been classified or described as “symptoms of menopause”. But does this description diminish the significance of these manifestations? Labeling hot flashes and night sweats as symptoms of menopause in some ways implies they are merely bothersome symptoms that should be tolerated or treated until they resolve rather than manifestations of one or several underlying pathophysiological processes. Is it time for the scientific and medical community to change the description of hot flashes and night sweats from “menopausal symptoms” to a term that describes the potential underlying pathophysiological phenomenon of autonomic neurovascular dysregulation?

Historically, hot flashes and night sweats have been successfully treated with estrogen in the form of either 17 β -estradiol (oral or transdermal preparations) or oral conjugated equine estrogens. Indeed, the practice guidelines from the Endocrine Society, the International Menopause Society, and the North American Menopause Society recommend the use of estrogen to relieve “vasomotor symptoms of menopause.”(1-3) In this line of thinking, vasomotor symptoms represent a chronic condition that is successfully treated with menopausal hormone therapy (MHT). However, the underlying pathophysiological mechanism accounting for and sustaining vasomotor or autonomic neurovascular dysregulation remains incompletely understood.(4)

In studies of women around the world, the prevalence of hot flashes varies across the menopausal transition.(5, 6) In three large, contemporary studies of women who experience hot flashes in the menopausal transition[the Australian Longitudinal Study of Women's Health (ALSWH), the Medical Research Council National Survey of Health and Development (1946 British birth cohort study), and the Study of Women Across the Nation (SWAN, USA)](7-10), four patterns can be identified based on onset, severity, and duration (Figure). In spite of differences in data reporting and terminology used to describe the patterns, their similarity across countries makes it unlikely that the patterns are solely explained by socioeconomic or cultural factors. If these four patterns reflect differences in neuro-regulatory processes or differences in vasomotor instability across women, it may be possible to separate the biological causes from the environmental and socioeconomic causes. In addition, these patterns might differentially associate with other chronic conditions of aging such as sleep disturbances, cognitive and mood disorders, cardiovascular disease, and osteoporosis.(11-13) Thus, we hypothesize that the changing hormonal environment of menopause (natural or surgically induced by oophorectomy) unmasks differences in the

autonomic neurovascular control mechanisms that put an individual woman at risk for chronic conditions of aging. These observations can be explained by the unifying hypothesis of eu-estrogenemia proposed by Turner and Kebler.(14) This hypothesis is also supported by the variability in clinical manifestations of aging observed in women following bilateral oophorectomy(15), and by the differences in sleep-related blood pressure variability in menopausal women with insomnia.(16).

Studies of the mechanisms underlying the expression of vasomotor instability in women have been hampered by the absence of animal models that recapitulate natural menopause and the various vasomotor patterns in relation to sleep and behavior (mood).(17-19) In addition, progress has been slowed by the lack of convenient, reliable, and standardized tools to objectively monitor vasomotor patterns in women(20), especially in a routine clinical setting, by the lack of standard terminology to describe and report the patterns (see figure), and by the lack of funding for longitudinal studies.

The presence and the severity of hot flashes and night sweats in clinical settings and clinical studies are usually self-reported using a Likert scale classifying the symptoms as none, mild, moderate, or severe. Such reporting may reflect cultural attitudes and care-giver bias in assessing the data and, therefore, does not inform the investigator or the treating physicians of the frequency, pattern, or timing of the events. Nevertheless, even with such an unsophisticated tool, significant associations of “severe” vasomotor patterns with sleep disturbances have been identified. Women with severe vasomotor patterns may need to undergo additional testing for sleep disorders such as obstructive sleep apnea or restless leg syndrome, particularly if the vasomotor symptom but not the sleep disturbances are diminished by MHT.(21-23) In general, the severity of vasomotor symptoms is also associated with an increased risk of cardiovascular disease including endothelial dysfunction, development of carotid intima media thickness, coronary artery calcification, cardiac microvascular disease, and adverse cardiac events.(24-27) However, the risk may vary with both the age of onset of menopause and the severity and type of the vasomotor disturbance (daytime hot flashes, night sweats or both.)(1, 12, 13, 20, 28-30)

Several genetic variants for enzymes involved with estrogen metabolism and for estrogen receptors are associated with onset of menopause and with the presence and severity of vasomotor instability.(11, 31-34) However, it is not known what fraction of the variability in phenotypes, including women who do not experience vasomotor symptoms, is explained by these genetic variants in the estrogen synthesis and signaling pathways, or the contribution of other variants such as those in genes within the noradrenergic or serotonergic signaling pathways. There is a need for additional case-control studies of large numbers of women for whom the absence or the presence, as well as the patterns of vasomotor symptoms, are known. In spite of the limitations of genetic studies, the development of a genotypic algorithm may help health care providers to select the most appropriate dose and formulations of MHT to target specific outcomes.

Given the associations between the presence, timing of onset, severity, and duration of hot flashes and the risk of several neurological conditions (sleep, mood, and cognition) and of cardiovascular disease, it is time to investigate the pathophysiological mechanisms

underlying the four patterns of vasomotor symptoms more closely in terms of the central pathways that are involved. One such pathway is the hypothalamic-pituitary axis involving the KNDy neurons (kisspeptin, neurokinin B, and dynorphin) projecting to the hypothalamic site of thermoregulation.(35) Indeed, neurokinin B receptor antagonists reduced self-reported hot flashes by 45% over a 90 day period in a small group of women.(36) In the future, it will be important to understand whether these drugs are effective in reducing all patterns of vasomotor symptoms, their efficacy on daytime hot flashes compared to night sweats, and their possible effects on sleep and mood.

Interconnections of the hypothalamus with other areas of the brain related to sleep and mood need to be investigated more closely because vasomotor symptoms can be treated with drugs affecting the serotonin system (i.e., selective serotonin reuptake inhibitors, SSRIs), the noradrenergic system (i.e., α_2 -adrenergic agonists), the cholinergic system, and the gabanergic system.(37) However, these treatments have not been explored in relation to patterns of vasomotor symptoms, hormonal status, or risk for chronic diseases of aging (i.e., osteoporosis, cardiovascular disease, and cognitive decline).

In addition to dissecting the interactions between central thermoregulatory pathways and sleep, a greater understanding of potential differences in the autonomic outflow from these centers (sympathetic and parasympathetic activation) and in the neuroeffector tissues is needed. In particular, further research is needed on patterns or changes in peripheral innervation and activation, neurotransmitter synthesis, adrenergic and cholinergic receptor responsiveness of the vascular smooth muscle, and on vascular smooth muscle sensitivity to vasodilatory processes mediated by the vascular endothelium including those processes requiring activation of guanylate cyclase.(38-40)

Devices to quantitatively monitor physiological parameters associated with hot flashes (skin resistance) are now available so that prospective studies can be designed to examine the relationships between genetic variants affecting hormone metabolism and hormone receptors, and the autonomic neurovascular regulatory processes manifesting as vasomotor symptoms.(41-43) A few key research questions for future inquiry are listed below:

- Is there a difference in autonomic function [perhaps measured by peripheral skin or muscle sympathetic nerve activity(44-46)] among women who experience different patterns of autonomic neurovascular dysregulation (none to severe)? How do these patterns relate to the risk of cardiovascular disease, osteoporosis, sleep and mood disorders, or cognitive decline?
- Is the difference in autonomic function across women associated with their age of onset of menopause or their genomic profile for estrogen metabolism and signaling? How do these genotypes relate to patterns of autonomic neurovascular dysregulation?
- Can more convenient and sensitive monitoring devices be developed to assess patterns of autonomic neurovascular dysregulation (vasomotor symptoms)?
- How does the risk for chronic disease change with an individualized MHT dosing regimen?

Considering vasomotor disturbances as manifestations of one or several underlying pathophysiological processes, rather than as a “symptom” of menopause, shifts the focus of scientists and clinicians toward the need to mitigate future chronic disease risk (cardiovascular disease, dementia, and osteoporosis).

Conclusion

Classifying hot flashes and night sweats as symptoms of menopause rather than as manifestations of an underlying autonomic and vascular dysregulation has hampered scientific investigation into the mechanisms controlling these phenomena, and has delayed the understanding of different aging trajectories in women due to estrogen deficiency. “Autonomic neurovascular dysregulation” may not be the only or final term to describe these physiological responses. However, the name describes a physiological phenomenon that can help to focus attention and research on the underlying control mechanisms.

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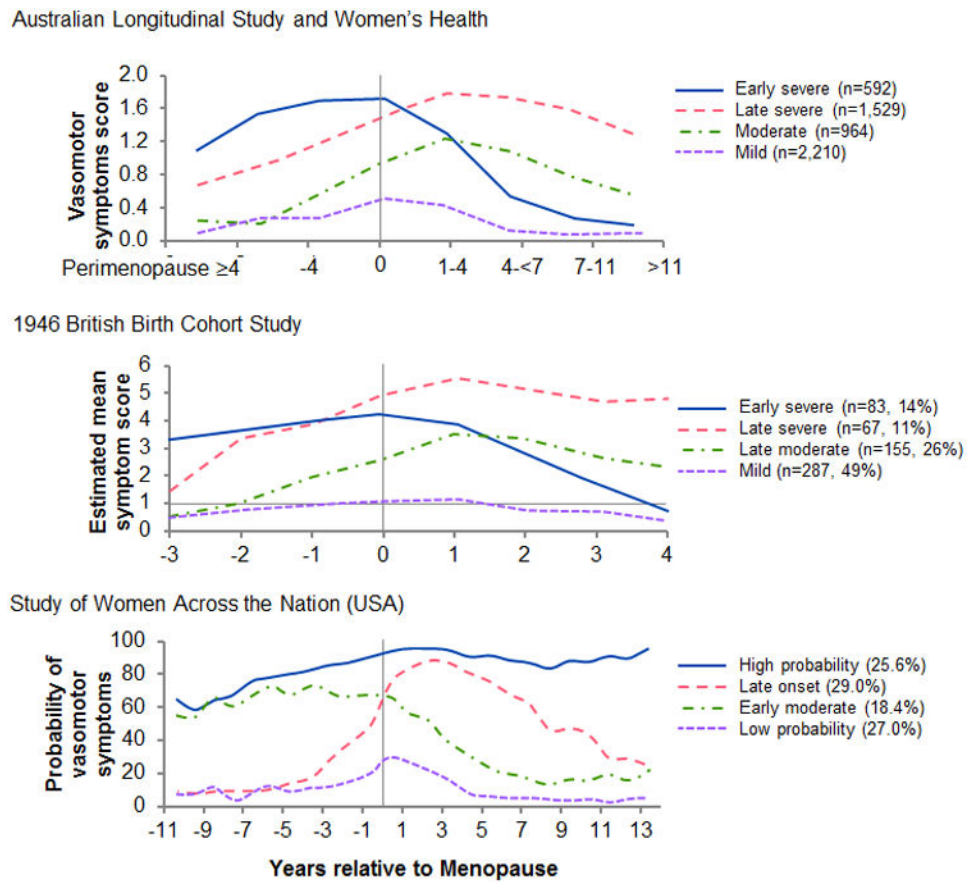


Figure. Patterns of vasomotor disturbances defined as a composite including hot flashes and night sweats reported by women transitioning through menopause in three distinct geographical regions: Australia, Great Britain, and the United States. Patterns were derived from data presented in Figure 2b of reference 5 (top panel), Figure 3 of reference 6 (middle panel), and Figure 1 of reference 7 (bottom panel). (Figures are reproduced with permission.)