Sex Differences in VCI

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The impacts of sex differences on the biology of various organ systems and the influences of sex hormones on modulating health and disease have become increasingly relevant in clinical and biomedical research. A growing body of evidence has recently suggested fundamental sex differences in cardiovascular and cognitive function, including anatomy, pathophysiology, incidence and age of disease onset, symptoms affecting disease diagnosis, disease severity, progression, and treatment responses and outcomes. Atrial fibrillation (AF) is currently recognized as the most prevalent sustained arrhythmia and might contribute to the pathogenesis and progression of vascular cognitive impairment (VCI), including a range of cognitive deficits, from mild cognitive impairment to dementia.

sex differences sex hormones atrial fibrillation

1. Introduction

Sex hormones are steroid hormones that bind to sex hormone receptors; they are also referred to as sex steroids, gonadocorticoids, and gonadal steroids. Androgens and estrogens—the main sex hormones—act differently in males and females. Hormonal effects are primarily mediated by rapid nongenomic actions through membrane-associated receptor signaling cascades and by slow genomic actions via classical sex steroid receptors [1][2].

17β-Estradiol, also referred to as E2, is the most potent and prevalent form of estrogen; it is synthesized mainly in granulosa cells of the female ovaries and male Sertoli cells. Estrogen synthesis also occurs locally in the central nervous system from cholesterols or is converted from aromatizing androgens in presynaptic terminals [2]. Testosterone is converted to E2 via P450 aromatase in the hypothalamus of men, where mental/social sex determination occurs [3]. E2 exerts its physiological effects by activating various estrogen receptors (ERs), which have at least three forms: ERα, ERβ, and membrane-bound G protein-coupled ER (GPR30/GPER1) [4]. ERα and ERβ are well-studied nuclear steroid receptors that are associated with the cytoplasm, plasma membrane, and nucleus in vascular smooth muscle cells, cardiomyocytes, and vascular endothelial cells in the mammalian cardiovascular system [5][6][7]. Both types of ER function as ligand-activated transcription factors and therefore exert long-term genomic effects by modulating gene expression through direct interaction with highly conserved DNA-binding domains of nuclear ERs and estrogen response elements located near the promoter or enhancer regions of estrogen-targeted genes [4]. GPR30/GPER1, which is highly expressed in the hypothalamic–pituitary–adrenal axis, has been shown to act as a membrane ER mediating the nongenomic effects of E2 [8]. GPR30/GPER1 signaling has been shown to improve spatial memory, possibly via neurotransmitter release and generation of new spines on hippocampal neurons [8]. Moreover, GPER1 activation leads to the phosphorylation of the classical

intracellular ERα, suggesting that crosstalk with ERα contributes to anxiety and social behaviors, such as social memory and lordosis behavior, in mice [8].

Testosterone, the principle androgen, is mainly synthesized in male testicular Leydig cells and female ovarian theca cells and secreted into the blood stream. It is converted into a more potent androgen, dihydrotestosterone (DHT), by 5α-reductase in the testes and prostate (in men), ovaries (in women), skin, and other parts of the body. Both androgens serve as ligands for androgen receptor (AR), a ligand-dependent transcription factor and a member of the nuclear receptor gene superfamily that mediates androgen signaling in males and females [9]. Upon binding to testosterone or DHT, AR undergoes conformational changes to recruit several essential co-regulators, translocates into the nucleus, and regulates the actions of genomic androgen by interacting with androgen response elements (AREs) located near the promoter or enhancer regions of androgen-targeted genes [1]. Numerous AR co-regulators play vital roles in AR stability and transcription, which influence proteasome degradation and affect their ligand and DNA-binding capabilities [1]. AR is expressed in several vascular cell types, such as smooth muscle cells, endothelial cells, and blood cells including macrophages and platelets [10][11]. Several physiological regulators of cardiovascular function, such as nitric oxide release, Ca^{2+} mobilization, vascular apoptosis, hypertrophy, calcification, senescence, and reactive oxygen species generation, are influenced by nongenomic androgen actions [11].

In the heart and brain of both males and females, sex hormones regulate the structure and function of cardiovascular and neural systems to modulate behavior and disease patterns at distinct molecular and cellular levels via the actions of sex hormone receptors [12]. Sex differences have been observed in diseases such as atrial fibrillation (AF) and vascular cognitive impairment (VCI). These sex differences and differential responses to sex hormones in the diseases of heart and brain, which influence cardiovascular and cognitive functions, were previously considered as separate events. Now, emerging evidences indicate that hormonal communications between the heart and brain occurs partly through the cerebral vasculature, where sex hormone signaling may act differently in male and female via the genomic and nongenomic actions of sex hormone receptor.

2. Sex Differences in VCI

2.1. Sex Differences in the Epidemiology and Clinical Outcomes of VCI

Cerebrovascular disease (CVD), the second-most common cause of cognitive impairment (CI) and dementia, frequently contributes to cognitive decline in neurodegenerative dementia. VCI is associated with vascular disorders that may coexist with neurodegeneration [13][14][15] and includes milder forms of CI and vascular dementia (VaD). Many patients with CVD develop several cognitive disabilities. Some studies suggested that male sex is a risk factor for CI [16][17]; others found that female sex is predictive of the increased risk of CI [18][19]. Although dementia disproportionally affects females, there are conflicting findings on the influence of sex on the incidence and prevalence of VCI [20]. Sex-related differences in risk factors, cognitive profiles, rates of deterioration, pathogenesis, and outcomes remain unknown. Evidence has revealed a sex-specific pattern in the incidence of CVD, with women having lower incidence rates of both ischemic stroke and intracerebral hemorrhage (ICH) than

men [21]. Among 860 patients with CVD, significantly more women than men had poor cognitive performance (approximately 15% difference) [20]. Despite the similar incidence of VCI between women and men [20], women tend to experience more severe strokes [22], whereas men frequently experience their first stroke earlier [22]. Risk factors for CVD such as AF, HF, myocardial infarction, high blood pressure, hyperlipidemia, obesity, and diabetes mellitus (DM) are more common among men [23][24][25]; however, the incidence rates of dementia associated with these risk factors are conflicting [23][24]. Some studies reported no significant difference in the risk for VCI between men and women [26][27][28], whereas others suggested that men had significantly higher incidences of VCI [29][30][31]. Studies have found that women experience poorer functional and cognitive decline after stroke than men [32][33][34]. Women had a greater risk for dementia among individuals with DM [24]. In a meta-analysis, sex differences in the prevalence of VCI were associated with age: VCI was more prevalent among men aged <79 but was more prevalent among women aged >85 [35].

Sex differences in the efficacy of stroke treatment have also been reported. Aspirin was found to be more effective in preventing stroke in women than in men [36], whereas warfarin was more effective for AF in men than in women [37]. Considering that therapeutic efficacy against stroke is implicated in the prognosis of VCI, the influence of sex differences is crucial in the clinical outcome of VCI. Sex differences also influence the efficacy of nonpharmacological interventions against VCI [38]. Thus, sex differences in the efficacy of stroke treatment should be determined.

As women tend to experience more severe stroke than men, they would have a higher incidence of VCI than men [39]. Within the first 3 weeks, the most important predictor of long-term functional outcome in patients with stroke is memory, which is associated with the medial temporal lobe (MTL) volume [40]. As men reportedly have larger MTLs than women [41], sex differences might affect the prognosis of VCI considering their influence on brain morphology. However, executive function was found to be a predictor of functional outcome and is associated with prefrontal volume [42]. The results regarding the influence of cognitive sex differences on VCI prognosis are inconsistent. Thus, the modulating effect of sex differences on the relationship between cortical volume and VCI prognosis remains unclear. Patients with VCI exhibiting memory, visuospatial, and executive impairments show significantly poorer global cognitive function, as assessed using the Mini-Mental State Examination (MMSE) [43]. Executive dysfunction, which can be measured using the Trail-Making Test A, was demonstrated to be a predictor of the modified Barthel index in patients with VCI [43].

Acetylcholinesterase inhibitors (AChEIs) can improve cognitive function in patients with VCI [44]. Cholinergic augmentation led to significant improvements in MMSE scores after 4 weeks in patients with post-stroke CI and VCI [44]. The neural system and cholinergic pathways, which comprise the basal forebrain, substantia innominata, striatum, cerebral cortex, some brainstem nuclei, and spinal motor neurons [45], are vulnerable to vascular damage, which can cause CI. It has been suggested that AChEIs modulate CI by compensating for the lack of intracerebral cholinergic neurotransmitters by inhibiting acetylcholine hydrolysis. This has been considered an effective treatment pathway in patients with post-stroke CI and VaD [46]. Sex differences in pharmacological effects have been associated with higher sensitivity to the toxic effects of organophosphate cholinesterase inhibitors in males [47]. Therefore, older males and females might respond differently to AChEIs because of either sex-specific

differences in the structure and function of the cholinergic system, pharmacokinetics, memory function, or the effects of aging or AD on such processes [47].

3. Pathophysiology of Sex Differences in VCI

3.1. Sex Differences in Brain Structure and Function among Individuals with VCI

To determine the influence of sex differences on VCI, the pathogenesis of stroke [22], cerebral infarction [22], intracranial hemorrhage [22], efficacy of secondary prevention [36][37], and risk factors for cerebral atherosclerosis should be considered [23][24][25], along with structural and functional sex differences in the brain [48]. Regional sex differences in brain volume might be implicated in sex-specific CI during VCI.

Sex differences have been demonstrated in several cognitive tasks. Men have been reported to outperform women in spatial ability [49], whereas women outperform men in verbal ability [50]. Cognitive sex differences have been associated with differences in structural and functional brain organization.

While men have higher metabolism within the temporal-limbic areas, women have higher metabolism in the cingulate areas [51]. Men experience increased functional connectivity (FC) within and among parietal-occipital regions, as evaluated using resting-state functional magnetic resonance imaging, whereas women experience increased FC within and among frontotemporal regions [52][53]. Moreover, men have stronger inter-network FC, whereas women have stronger intra-network FC [54].

Sex differences also contribute to variability in brain morphology. Men have significantly larger frontal, temporal, left parietal, and insula areas than women [55]. Women exhibit a higher gray matter (GM)/white matter (WM) ratio in the parietal cortex [56][57], cingulate gyrus [41][58], and insula [58]. Men have increased GM volumes in the MTL and entorhinal cortex, whereas women have increased GM volumes in the right inferior frontal and cingulate gyri [41]. After correcting for whole-GM volume, women exhibited greater GM percentages in the dorsolateral prefrontal cortex and superior temporal gyrus than men [59], implying that women have better language-related abilities than men [59]. Regarding WM structures, women have significantly lower fractional anisotropy in the right deep temporal regions [60].

3.2. Sex Differences in Risk Factors for VCI

Although risk factors for CVD such as DM, obesity, and hypertension are more common in men [23][24][25], they more adversely affect women [25]. However, hyperlipidemia, MI, AF, and HF show higher influence in men [25]. While men are more likely to experience stroke than premenopausal women, similar incidences of stroke have been recorded between men and postmenopausal women [22][61]. Sex differences according to the type of stroke have also been reported: brain infarctions and ICHs are more common in men, whereas subarachnoid hemorrhages are more common in women [22].

Women are more prone to obesity and obesity-related DM, which increases the risk of VCI [62][63]. Therefore, sex differences in the effects of type 2 DM on VCI suggest that women are more adversely affected than men. More women are overweight or obese after the age of 45 years, whereas more males are overweight at a younger age. Besides age, the influence of sex differences on body mass index (BMI), body fat distribution, brown adipose tissue, metabolic syndrome, and adipokines leads to an increased risk of DM and DM-associated VCI in women [63].

Obesity is another important risk factor for VCI. The effect of BMI on VCI is more pronounced in women than in men. Higher midlife BMI has been associated with increased vascular risk factors, changes in adipokines (plasminogen activator inhibitor-1, IL-6, TNF-α, angiotensinogen, adiponectin, and leptin), and brain structure alteration [64], whereas lower BMI later in life has been associated with neurodegenerative processes [65].

Besides DM and obesity, sex differences also affect hyperlipidemia. Decreased high-density lipoprotein (HDL) and increased triglyceride levels in men have been associated with an increased risk for all-cause dementia [66]. In women, low HDL levels have been associated with increased WM lesions and silent brain infarcts [67]. Large vessel strokes (macroangiopathy and arteriosclerosis), small vessel disease (microangiopathy and arteriolosclerosis), and microhemorrhages are the main causes of VCI [68]. Therefore, the lower HDL levels in women may explain their higher risk for VCI. Given that the genetic effects of APOE4 are associated with lipoprotein metabolism, studies have found that higher levels of APOE4 allele are associated with a higher risk of VCI [69][70].

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