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Review Article

Sex Differences in Neurodegenerative Diseases

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Abstract

There is a clear sex bias in the incidence, prevalence and outcome of many neurodegenerative disorders. The high incidence of these diseases in an increasingly aging population has raised interest in understanding the relevance of sex in the progression of these diseases and their treatment. Important sex differences have been reported in autoimmune, neurodegenerative and mood related disorders.

In this review, we take an insight in the differential evolution of some neurodegenerative diseases depending on the sex, highlighting the importance of gonadal hormones in this process, and the implications of a proper understanding of the mechanism underlying these differences for the therapeutic strategies for the prevention and treatment of these diseases.

Introduction

Neurological and neurodegenerative diseases encompass a diverse series of diseases that do not only imply brain impairments, but also affect the overall well-being of the patient. These are characterized by progressive loss of neurons (or subsets of neurons) in the Central Nervous System (CNS), that go along with rapid and usually irreversible loss of crucial cognitive and motor functions. Most of these diseases are associated with age, as their incidence increases in the elder.

The last reports of the World Health Organization (WHO) have highlighted that there are over 1 billion people affected by neurological disorders. Such a high incidence of these diseases in an increasingly aging population has raised the interest in the understanding of the importance of sex in the progression of these diseases and their treatment.

Brain development and adult brain structure, function, and biochemistry strongly differ by sex [1]. These sex differences are initiated through sex-determining genes and fetal hormonal programming. Such differences in the brain anatomy and genetic network of the healthy human brain are likely to underlie the pronounced sex differences in susceptibility, progression, pathological scores and severity of several diseases [1-4]. Exploring sexual dimorphisms in the brain is key to understand the importance of sex in the different stages of the disease and might also have important therapeutic implications for the treatment of many neurological and psychiatric diseases.

Sex Differences in Neurodegenerative Diseases

There is a striking sex bias in the incidence, severity, progression and outcome of several neurological disorders [5]. Alzheimer's disease (AD) has a higher prevalence in women above 65 years old (1.6-3:1 ratio compared to men), and also courses with a greater cognitive deterioration [6-8]. However, men have a higher incidence of Parkinson's disease (PD) (3.5:1 compared to women). Besides, women suffering from PD show a slower rate of decline than men do [9,10].

As for autoimmune diseases, women are also more prone to suffer from multiple sclerosis (2-3:1 ratio compared to men), however, the progression of the disease is faster in men [11,12]. On the contrary, in the case of some motor neuron diseases, such as amyotrophic lateral sclerosis, men have a higher prevalence and show an earlier onset (1.6:1 compared to women), but women suffering from this disease show a worse survival than men [13,14].

Mood related disorders, such as depression or anxiety disorders, also have a higher prevalence in women (2:1); moreover, they show increased severity of the symptoms, and a higher incidence of subclinical depression [15,16]. On the other hand, men show a higher prevalence (3:1 compared to women) in attention deficit hyperactivity disorder, which goes along with a severe deficiency in motor skills and higher distractibility in boys than in girls [17-20]. They also have a higher incidence of schizophrenia (1.4:1) and an earlier onset of the disease as well. Men show a poor prognosis with severe symptoms and worse response to antipsychotic drugs than women [21-23].

Autism spectrum disorders have a higher incidence and prevalence in boys than in girls (4:1), however, this ratio is quite controversial, since some researchers have shown that females have less severe stereotyped and repetitive behaviors, which may lead to a bias in the diagnoses of this disease [24-26].

Sex dimorphism and Alzheimer's disease (AD)

AD is a chronic neurodegenerative disease that affects around 6% of people over 65 years of age, although there is an early-onset incidence of 4% to 5% of the cases. It is the cause of 60% to 70% of dementia cases. The symptoms range from memory decline to problems with language, disorientation, mood swings and loss of motivation among others.

As mentioned above, there is a striking sex bias in the incidence and prevalence of this disease. The high incidence of AD in the global population has favored an extensive study of the sex differences not only in the incidence of the disease, but also in terms of localized brain changes and brain function. Recent studies show that women diagnosed with AD experience a faster progression of hippocampal atrophy than men [27], whereas men are more prone to progress to AD in the presence of severe peri-ventricular white matter hyperintensities and reduced global cognitive performance [28].

Clinical presentations also differ between men and women, showing men more aggressive behaviors, comorbidity, and higher mortality than women; while women tend to suffer from more affective symptoms and disability but longer survival [29].

These differences indicate that there might be an urge for different management strategies to treat men or women suffering from AD. From the perspective of treatment, emerging evidence also points to the possibility that sex-specific genetic and hormonal factors contribute to variance in clinical efficacy.

Overlooking of sex interaction in previous studies might be the explanation for inconsistencies in the results of the importance of genetic factors, such as that of the APOE- ϵ 4 allele relevance [30]. Interestingly, recent studies taking sex as a factor showed that variants of the o-estrogen receptor α gene (ESR1) caused an improved response to acetyl cholinesterase inhibitor treatment in women with AD [31].

Therefore, specific therapies for AD patients, considering sex as a relevant differential factor may lead to a better outcome in the treatment of these patients.

Sex dimorphism in Parkinson's disease (PD)

PD is the second most common neurodegenerative disorder, affecting approximately 0.3% of people in the developed world. Its incidence rises rapidly to 3% for individuals over the age of 65 years, to demonstrate that advanced age comprises a major risk factor [32]. PD is a movement disorder characterized by motor symptoms such as bradykinesia with rigidity, tremor at rest, gait disturbances and difficulty in swallowing and producing speech. There are also non-motor symptoms associated with this disease, which include anxiety, depression, insomnia, dementia, autonomic dysfunction and constipation, which can often reduce patients' quality of life even more significantly than motor aspects [33].

After aging, epidemiological studies have revealed that the male sex is a prominent risk factor for developing PD at all ages, for all nationalities studied. Studies on sex hormones being critical drivers of sex differences in disease susceptibility are especially focused in the effects of 17β -estradiol (E2), the most abundant estrogen in non-pregnant mammals, which is widely recognized to have neuro

protective actions and, therefore, may confer the advantage in diseases where women generally fare better, such as PD [34]. Indeed, women who underwent bilateral ovariectomy before menopause have an increased risk of developing PD [35].

Compelling evidence suggests that biological sex differences in the neurosteroidogenic path way may underlie some differences in vulnerability, in PD experimental models. It could also account for the sexually dimorphic actions of estradiol, which protects females against striatal DA loss in experimental PD, but fails to protect, and may even worsen, striatal lesions in males.

Current dopamine replacement strategies ameliorate the symptoms of PD, both in men and women, however, these findings highlight the need for sex-specific treatments, which demands a better understanding of sex dimorphisms. They also open up the potential to exploit hormone-based therapies as a novel approach to develop new treatments, which could delay the progression of the disease. However, this will require further research on how the endogenous hormonal milieu interacts with other sex-specific factors that are also important for the evolution of PD [32,36,37].

Sex dimorphism and stroke

There are clinically well-recognized sex differences in ischemic stroke. Even though the overall incidence of stroke is higher in men than in women, up to the age of 80 years, when stroke incidence increases dramatically in women, women account for 60.6% of stroke deaths [38]. Besides, the incidence of recurrent stroke is higher in women both at younger and older ages.

Sex differences in stroke are most likely due to a multitude of interacting factors, some of which are often not considered in large epidemiological databases. For instance, women have higher incidence of some risk factors such as central adiposity, endogenous sex hormones and psychological factors (depression) than men [39]. Many of the deleterious effects of aging on stroke outcome in females can be replicated in experimental models by ovariectomy, suggesting a key role of female gonadal hormones in the incidence of this disease.

Importance of gonadal hormones

Estrogen and testosterone are the major sex hormones in humans. These hormones bind to specific steroid hormone receptors, which comprise a wide range of locations in the cell: nuclear, cytosolic and in the cell surface (G protein-coupled receptors and ion channels). Depending on their location and downstream gene activation, sex hormones trigger long-term or short-term effects in the cells.

Prenatally or in early postnatal life, when there is a peak in the testosterone levels in males, these hormones exert organizational effects, which are permanent and independent of acute circulating hormone levels [40,41]. During development, after testicular differentiation in males, Leydig cells start producing testosterone, which is then transformed by the neuronal aromatase to 17β -estradiol. This estrogen exerts masculinizing actions through estrogen receptors. Besides this endogenous synthesis of estrogens in the male brain, both male and female brains are exposed to high levels of estrogens produced by the placenta and the mother. However, the differential organization of the female brain occurs due to the presence of alpha-fetoprotein in the plasma, which binds circulating estrogens, and

prevents estrogen binding to the cells, hence protecting the female brain from the masculinizing effects of estrogens [42,43].

Later in life, estrogen and testosterone have activation effects, which are dependent on the continued production of gonadal hormones and disappear whenever gonadal function is compromised [41].

Normally, activational effects are constrained by earlier organizational effects. However, there are interactions between organizational and activational effects of gonadal hormones. Indeed, the same hormone at different time points in development leads first to brain programming early in life, and later can directly activate those traits. Both, organizational and activational effects of gonadal steroid hormones have been shown to be implicated in the increased risk of affective disorders in women.

There has been an extensive interest in understanding the interactions of sex chromosomes and gonadal hormones in the regulatory and inductive mechanisms of neurodegenerative disorders, focusing on the autoimmune component of these diseases [44,45]. Some authors have tried to link these sex differences in the disease prevalence and resistance to the differential immune responses of males and females. Generally, females exhibit enhanced immune responses than males, and they also present increased resistance to some diseases and infections. Beneficial as it might seem, this efficient peripheral immune response may also favor the development of autoimmune diseases [46,47].

Neuroinflammatory processes, such as overproduction of pro-inflammatory cytokines, contribute to the pathogenesis, clinical onset and progression of several neurological diseases. Indeed, inflammatory mediators are synthesized at the sites of neurodegeneration in stroke [48,49], multiple sclerosis [50,51], amyotrophic lateral sclerosis [52], AD [53,54] and PD [55]. Notably, inhibition of neuroinflammation (either mediated by steroids or non-steroidal drugs) goes along with less neurodegeneration [56,57].

Sex steroids, principally 17 β -estradiol, influence the immune function and inflammatory processes in the brain [58,59]. Indeed, estrogens decrease the activation of the neuroinflammatory cascade at the cellular level and further inhibit the release of molecular factors, blocking two essential events in the maintenance and progression of the inflammatory response [60,61]. The anti-inflammatory action of estrogens may represent an important mechanism underlying the neuroprotective effects exerted by these hormones in several neurological diseases. Moreover, this hormonal factor has been postulated as a plausible candidate to explain the sexual dimorphism in the CNS disorders that course with neuro inflammation [62-65].

Consequently, research of sex differences in these diseases has been focused on the direct and indirect immunomodulatory actions of sex steroid hormones [66-69]. Low doses of exogenous estradiol exert immune enhancing effect on humoral immunity; however, high doses suppress cell-mediated immunity [70-72]. Exogenous testosterone, on the other hand, has a depressor effect on both humoral and cell-mediated immunity, increasing susceptibility to infection [73-75].

As we have previously mentioned, there is a widespread location of sex hormone receptors, in the cells, but there is also a differential overall brain expression of steroid receptors, which has been

well described in all prenatal, postnatal and adult brains [76-78]. Therefore, any sex-specific variations in the expression of gonadal hormone receptors might contribute to the susceptibility to maternal or fetal sex-steroid hormone levels, and the risk to the development of neurological diseases through life.

Genetics and sex dimorphism

We cannot obviate the genetic component of some of these neurodegenerative disorders. Notably, certain genetic mutations might partially explain the sexually dimorphic incidence associated with some of these diseases, while not others.

As we have mentioned above, autism spectrum disorders have a higher prevalence in male. Recent research has shown that females have a higher threshold for developing autism, this is, and they need a higher mutational load than their male counterparts to have the same level of affection by the disease [79]. A plausible explanation is that some autism spectrum disorders forms are an X-linked disorders and females may be protected due to a normal copy of the mutated gene in the second X-chromosome. One autism-related gene located in the X- chromosome is FMR1. The encoded protein is implicated in synaptic plasticity, therefore, malfunction of this protein leads to functional impairments in the brain [80].

Heritable forms of A Dare also related to gene mutations. Mutations in APP, PSEN1 and PSEN2 genes have been shown to be the cause of heritable early-onset Alzheimer's disease [81]. Mutations in the apolipoprotein A (APOE e4) gene, in chromosome 19, or some TREM2 gene variants, in chromosome 6, have been shown to be risk factors to develop late-onset disease [82,83]. However, the role of genetic mutation in sex differences in the pathology or incidence of the disease remains to be clarified.

There are also some genetic contributors to PD, such as mutations on Leucine-Rich Repeat Kinase 2 (LRRK2, also known as dardarin), alpha-synuclein clumping (SNCA), Glucocerebrosidase (GBA) and Parkin (implicated in protein degradation), or DJ-1 and PTEN-induced putative kinase 1 (PINK1) in the mitochondria genes (implicated in responses to oxidative stress) [84-86].

However, the incidence of the heritable forms of these diseases is very low, compared to the overall incidence of the disease (from 1-8% of the total patients). The etiology of sporadic forms of neurodegenerative disorders is multifactorial, and might involve genetic, environmental, sex factors and others.

Other risk factors

In addition to genetic or brain-based vulnerabilities, broader societal factors also have roles in the risk, progression, and outcome of neurodegenerative disorders. This risk has been extensively highlighted in the case of dementias. Education and occupation levels have also repeatedly been shown to affect the risk of dementia and for which substantial inequalities have existed between the sexes in previous generations [87].

Behavioral uses and life-style also affect the incidence of neurodegenerative disorders. Interestingly, sex differences in life-style may contribute to the sex differences seen in AD and PD, which could interact with a genetic predisposition [65,88], supporting the multiple hit hypothesis for developing PD [89].

Recent studies show that a healthier diet and regular exercise are linked with a delayed onset and milder symptomatology of some neurodegenerative diseases. On the other hand, so called “bad habits”, such as smoking and alcohol use, which also affect vascularity of the individuals, are risk factors for the aggressiveness of these disorders [90,91].

Conclusion

Clinical and pre-clinical studies demonstrate robust differences in male and female brain in both physiological and pathological conditions. The aim of this review is to point out that normal sex dimorphism in the brain might be key to understand the different incidence and outcome of several CNS-related diseases. Further research is required to understand and elucidate the mechanisms regulating sex-driven differences. However, better understanding of the biology underlying sex differences in the healthy and diseased brain will enable improved therapeutic strategies for the prevention and treatment of sex-biased neurological diseases.

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