



Sexual and Reproductive Problems Associated with Neurodegenerative Disorders: A Narrative Review

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Authors

Seyed Mohammad Hadi Mirab
Ameneh Omidi*
Arezoo Dorikhani

Department of Anatomical Sciences,
Faculty of Medical Sciences, Tarbiat
Modares University, Tehran, Iran.

*Corresponding authors:

Ameneh Omidi
Department of Anatomical Sciences,
Faculty of Medical Sciences, Tarbiat
Modares University, Tehran, Iran.
Phone & Fax: +98(21) 82884887
PO Box: 14117-13116
a.omidi@modares.ac.ir
amenehomidi86@gmail.com

ABSTRACT

Neurological disorders are illnesses in which the function of neurons in the brain and spinal cord is disrupted. In neurodegenerative diseases, based on various factors such as the etiology of the disease, the patient's age, and the brain and/or spinal cord region involved, the affected person may face a wide variety of signs and symptoms. In numerous neurodegenerative disorders such as Alzheimer's disease (AD), Parkinson's disease (PD), and multiple sclerosis (MS), according to the disease pathobiology, some sexual and reproductive problems, like sexual dysfunction, low sperm quality, and sterility, have been raised. Although sexual and fertility issues could result in several individual complications and heavy social burdens, limited studies have addressed these topics. This narrative review highlights sexual and reproductive disabilities in several neurological disorders, such as spinal cord injury (SCI) and MS.

Keywords: neurodegenerative disease, hypothalamus-pituitary-gonadal axis, sexual dysfunction, fertility.

Abbreviations: AD: Alzheimer's disease; CNS: central nervous system; DAergic: dopaminergic; EAE: experimental autoimmune encephalomyelitis; FSH: follicle-stimulating hormone; GnRH: Gonadotropin-releasing hormone; HD: Huntington's disease; HPG: hypothalamus-pituitary-gonadal axis; LH: luteinizing hormone; MS: multiple sclerosis; PD: Parkinson's disease; SCI: spinal cord injury; SN: substantia nigra.

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BACKGROUND

With 4.47 million people suffering yearly, neurodegenerative diseases are expected to affect up to 135.46 people worldwide by 2030 [1]. In neurodegenerative diseases, depending on the affected area and the extent of the brain and spinal cord involvement, the patient shows different signs and symptoms [2]. Generally, the nervous system controls all body performances, so modest neurodegenerative disorders may significantly impact a patient's sexual functions and fertility. Although the issues related to sexual health and reproduction are critical, healthcare researchers give less attention to patients who have undergone neurological accidents. These problems can severely overshadow a person's life from various

aspects, mainly sexual relationships and psychological status [3].

Several neuroanatomical structures, such as the spinal tracts, hypothalamus, and pituitary gland, which normally play an essential role in sexual function and fertility, are disrupted in neurodegenerative diseases. The hypothalamus-pituitary-gonadal (HPG) axis, which contributes to the maintenance of hormonal profile balance and many fundamental reproduction events as a consequence, would be affected by neurodegenerative conditions [4]. Gonadotropin-releasing hormone (GnRH), the most pivotal effector in the regulation of the reproductive biology in the brain, acts through this axis. GnRH is generated by the hypothalamus and bound to

specific gonadotroph receptors in the anterior pituitary. This coupling produces gonadotropins, including follicle-stimulating hormone (FSH) and luteinizing hormone (LH). The released gonadotropins bind to receptors on the gonads, prompting the secretion of sex steroid hormones like estrogen, progesterin, and androgens [4, 5].

Any neurobiological disruption in the sexual and fertility-related structures in the brain and spinal cord may result in a broad spectrum of individual and social problems in neurological patients [3]. In this article, the authors have attempted to focus more on the patient's sexual and fertility issues associated with the devastating neurological events.

The H&E-staining the coronal sections of the hippocampal CA3 area showed the regular structures of the CA3 region where the pyramidal cell layer neurons (P) have a uniform size and distribution in the control group. Each neuron had a rounded central nucleus with a prominent nucleolus (Figure A). The equivalent section from kindling group did not exhibit uniform size and distribution of pyramidal neurons. Hyperchromatic nuclei (thick arrows) and vacuolated cytoplasm were detected in kindling group (Figure B).

Interestingly, administration of hope extract to treatment groups could protect CA3 pyramidal neurons against PTZ kindling, so that their appearance was similar to control group (Figure C).

Spinal cord injury (SCI)

Spinal cord injuries are caused by various etiologies, such as congenital anomalies, traumatic events, and degenerative alterations [6]. Younger men are more typically affected by SCI, half of whom are under 35 [7]. Roughly 87 percent of these young spinal cord-injured men have sexual dysfunction [8]. Sexual dysfunction in patients suffering from SCI in men and women is diagnosed according to the evaluation of different sexual function indexes such as orgasm and satisfaction with intercourse [9]. Ejaculation, one of the main masculine indexes for assessing sexual health in men, is influenced by lower and upper SCI. The possibility of ejaculation in men with partial and complete lower SCI was 70 and 18 percent, respectively. In comparison, only 32

percent of subjects with partial and 4-11 percent with complete upper SCI could ejaculate [10]. The ability of the sperm to migrate swiftly and effectively toward their target destination is another significantly affected sexual function index [11]. Men with SCI have the most substantial losses in both volume and quality of sperm compared to healthy subjects. Data shows that the viability and motility of sperm in men with SCI have been lower than in normal subjects. In addition, other semen features, including necropermia and DNA fragmentation, have been identified in SCI individuals [12, 13].

Despite the several neurogenic sexual dysfunctions in women with SCI, fertility is still possible, but they may confront multiple complications, such as autonomic dysreflexia [14]. However, following the SCI crisis in women, neurochemical responses lead to increased prolactin. This stress-related hyperprolactinemia in spinal cord-injured women was strongly associated with amenorrhea and subsequent fertility problems [15].

Alzheimer's disease (AD)

AD is the most prevalent type of dementia in which neuron degeneration causes memory impairment, behavioral issues, and speech problems. The disease has affected 24 million individuals globally, which is expected to increase by more than fourfold by 2050. A combination of hereditary and environmental factors causes AD. The most prominent etiology of AD is aging, so the prevalence of AD in 80 old people is nine and four times more than in 65 and 70 [16, 17]. The hippocampal formation volume in AD patients is less than that of healthy subjects [18]. The pathophysiology of AD appears to be related to a loss in synaptic connectivity, extracellular plaque deposits of the beta-amyloid peptide, and intracellular nodes or plaques formed of phosphorylated microtubule-related proteins known as tau [19, 20]. Most evidence shows that dysregulation in the hormonal balance of the HPG axis, which mainly occurs with menopause and andropause, is related to promoting deteriorative changes in AD [21]. FSH, LH, and their receptors are predominantly present in limbic system neurons, especially hippocampal pyramidal neurons, which are particularly vulnerable to

harm in AD. The amount of LH in the cytoplasm of pyramidal neurons in individuals with AD has been higher compared to healthy people of the same age, resulting in an elevated LH in blood circulation in the patients. The accumulation of LH within pyramidal cortical neurons can be attributed to a spike in LH expression in response to GnRH, a decrease in LH intracellular breakdown, or an increase in LH release from external sources. Due to LH exorbitance, testosterone levels were lower in men affected by AD [22]. Although AD, as the most common proteinopathy, affects older individuals [23], because of the primary roles of sexual hormones in fertility, any disruption in the HPG axis that occurs in AD could potentially impact sexual behaviors and reproductive functions [24].

Parkinson's disease (PD)

PD is one of the most common chronic progressive neurodegenerative disorders. Loss of midbrain dopaminergic (DAergic) neurons in the substantia nigra (SN) presented as a primarily pathological etiology of PD; however, genetic, environmental, and aging are considered the main risk factors [25]. The SRY gene, Sex-determining Region of the Y chromosome, expressed in DAergic neurons of SN, makes males more vulnerable to PD commencement than women, but these gender differences decline with aging [26]. Clinically, PD is indicated by non-motor manifestations, such as anxiety and depression, and cardinal motor symptoms, like resting tremors and gait disturbances [27]. The commencement of PD typically occurs in late life [6]; in a way, the prevalence of PD is about 0.3% of individuals in developed countries, overgrowing to 3% in people older than 65 years. Although PD is the second most frequent age-related neurological disease that is infrequent in youthfulness [28], only 5% have an onset before 40 years old, but it may be faced in the childbearing age [29]. Nevertheless, PD, caused by the loss of DAergic neurons in SN, has nothing to do with infertility, and the association of PD with infertility sounds arbitrary [30].

Evaluating sexual health in PD patients revealed the existence of sexual dysfunction in 42.6-79% of men and 36-87.5% of females [31, 32]. However, a more recent systematic review on

assessments of sexual dysfunctions by the Arizona Sexual Experience Scale (ASEX) as a professional, easy, and fast tool that could apply in treatment guidelines, has declared the prevalence of these disorders, maybe even up to 90% and the most common type of SD was has been men's erectile dysfunction [33].

Although levodopa effectively treats PD movement symptoms, it often does not work for sexual dysfunction, which plays a fundamental role in declining quality of life. This evidence proposed that sexual dysfunction may occur through distinct pathobiological processes. According to PD patients' brain histopathological findings, hypothalamic dysfunction and, consequently, libido and erection-prompting dopamine-oxytocin pathways disruption can be considered the primary etiology for the sexual issues [34].

Epilepsy

One of the most prevalent neurological illnesses is epilepsy, in which the patient undergoes a series of frequent and sudden convulsions [35]. In addition to the epilepsy-related factors, some other items like medications and neuropsychological status may develop sexual dysfunctions in patients with epilepsy [36]. Sexual abnormalities, such as loss of libido, semen quality changes, impotency, and infertility, are typical clinical manifestations of epilepsy. However, it's still unclear if the symptoms of sexual dysfunction are related to epilepsy or anti-epileptic medicines like phenytoin, carbamazepine, and valproate [37]. There are some worries regarding the effects of these anti-epileptic treatments on the occurrence of sexual disorders symptoms in such ways that anti-epileptic medicines exert harmful impacts on reproduction by lowering testosterone levels, causing direct sperm toxicity, resulting in aberrant sperm shape, motility, and count, and some strange gonad consequences [38]. Testosterone synthesis failure, one of the fundamental causes of reproductive issues in anti-epileptic medicines consumers, occurs following HPG axis disruption [39].

Huntington's disease (HD)

HD is an autosomal dominant progressive neurodegenerative illness, manifesting as motor,

cognitive, and sexual dysfunction, caused by an over repetition of cytidine/ adenosine/ guanosine (CAG) trinucleotide in the Huntingtin (HTT) gene coding Huntington protein. Depending on the length of the over-repetition, the clinical phenotypes and age of HD onset vary in different patients [40]; however, males and females are affected equally [41]. Sexual abnormalities are displayed in about 75% and 85% of subjects with HD, females and males, respectively [42]. A previous study demonstrates the aberrant sexual behavior consequences of the HTT gene mutation in animal models. Moreover, the function of neural connections in developing HD-related illnesses is still debated [43]. In patients with HD, the loss of GnRH-releasing neurons through hypothalamic insults leads to HPG axis disruption. These events impair endocrine feedback mechanisms and the occurrence of gonadal atrophy and aberrant gametogenesis as consequences [44, 45]. According to tomographic investigations, hypothalamic insults are associated with decreased LH circulation in most with HD, even at the early stages of the condition [21, 46]. A study by Markianos M et al. revealed a potential relationship between a decrease in LH and testosterone with increased HD intensity [47]. However, since HD is autosomal dominant, the fertility issue is highly complex and challenging [48].

Multiple sclerosis (MS)

MS is a chronic demyelinating disease that affects the sheath wrapping around neural fibers in the central nervous system (CNS). MS is characterized by white matter lesions caused by inflammation and loss of the myelin sheath [49]. MS affects more than 2.3 million individuals worldwide, with 70% of those suffering between the ages of 20 and 40 [50, 51]. MS symptoms, including motor, cognitive, endocrine, and sexual dysfunction, vary depending on the affected area of the CNS. Since various sex hormones, such as progesterone, prolactin, and testosterone, have their specific receptors on the immunity cells, they could arouse these targets in distinct ways and different outcomes in the following [52, 53].

Sexual disturbances in MS patients manifest themselves in molecular, anatomical, physiological, and behavioral ways [54]. No

precise data indicates that women MS patients struggle with fertility concerns [55]. The prevalence of MS patients suffering from sexual issues is reported as about 70% in women and 50% to 90% in men. However, a more recent cross-sectional study indicates that sexual function impairment manifested in most MS patients (76%) [56]. Although both men and women are affected by sexual dysfunction, it significantly impacts men's quality of life [57]. Low libido (36–86%), orgasmic dysfunction (28–58%), vaginal dryness (8–40%), and a reduced feeling of touch (43–62%) are all indications of MS-related sexual dysfunction in females. On the other hand, decreased libido (37-86%), erectile dysfunction (34-80%), ejaculatory disorders (34-61%), and difficulty in attaining orgasm (29-64%) are symptoms in males that are thought to be associated with a drop in testosterone levels in MS patients [58].

The HPG axis would be disrupted under MS pathogenesis, influencing the sex hormone levels. According to clinical evidence, MS patients have a steroid hormone imbalance, with reduced estrogen levels accompanying increased gonadotropin levels in the early follicular phase. The quantity of released FSH is proportional to the ovary's ability to produce egg cells, i.e., ovarian reserve. So, due to gonadotropin imbalance, the ovarian reserve is depleted, resulting in poor egg quality and infertility [49].

In 2018, Muñoz-de-la-Torre, L. P et al. examined the blood levels of estradiol, progesterone, and testosterone in demyelinated and normal female rat groups divided into juvenile and adult subgroups. In demyelinating rats, compared to the control group, the data revealed a 21% rise in testosterone, a roughly 44% drop in follicle number with a 15% increase in atresia, and an 80% reduction in ovary catecholamines accumulation. In contrast to the control group, estradiol serum levels and the number of healthy follicles fell in adult demyelinated rats, although progesterone levels rose. However, the subgroups had no significant changes in the hormone serum levels [1].

A study on an experimental autoimmune encephalomyelitis (EAE) demyelination mouse model found that gender plays a vital role in the HPG axis' responses to neuroinflammation. The

results showed that serum testosterone in demyelinated male mice had a lower rate than in control animals. In male demyelinated mice, the inverted relationship between cytokine and testosterone serum level and LH serum level suggests that inflammatory cytokines inhibit testosterone production by directly influencing Leydig cells. On the other hand, there were no significant differences in serum estrogen of female demyelinated mice compared to healthy control animals [59].

Safarinezhad estimated gonadotropins and testosterone levels in 68 MS patients and 48 healthy participants. MS patients' basic levels of FSH and LH were significantly lower than healthy people. It revealed the average LH level considerably declined as the illness progressed, but the average FSH level remained nearly steady. On the other hand, the result of sex hormone evaluation and sperm analysis showed that there were reduced testosterone and sperm motility levels, as well as a significant change in sperm morphology. These results revealed that the more the illness progresses, the more HPG axis-related abnormalities emerge in MS patients [60]. Collectively, for several reasons, such as the heterogeneous nature of the disease, sexual dysfunctions are depicted at primary, secondary, and tertiary levels in MS patients. In brief, primary sexual disabilities arise directly from the demyelination of areas associated with sexual and reproductive functions. The secondary sexual dysfunctions originate from non-sexual factors like pain and fatigue. The tertiary level, similar to the secondary level, is indirectly caused by other factors, such as psychosocial non-sexual symptoms [61].

CONCLUSION

Neurological diseases are looked at as complex disorders, as well as some similarities, and each has its particular symptoms and pathogenesis, compromising from interactions between various factors such as genetics, environment, and aging. Sexual dysfunction and fertility problems are important in the life quality of neurodegenerative disease-affected people, the symptoms which are likely underestimated. Although the exact etiology of sexual dysfunction is still unknown, some studies revealed that neurodegenerative-

related sexual and reproductive issues generally occur due to the involvement and disruption of the HPG axis. This review allows us to conclude that sexual issues emerge depending on several candidates, like the nature of the neurodegenerative disease, sex differences, and the extent of intrinsic neuroprotection of patients. However, more studies are needed to understand the precise mechanism of sexual dysfunctions and infertility in neurodegenerative diseases and the application of appropriate treatment strategies.

DECLARATIONS

The authors declare no conflict of interest.

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