



## Review Article

### Neurodegenerative Diseases and Infertility

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#### Abstract

The exploration of potential connections between infertility cases and neurodegenerative diseases like Parkinson's or Alzheimer's, despite their unrelated nature. There are co-occurring processes between neurodegenerative diseases and infertility since both affect complex biological systems. Several genetic and physiological processes connect infertility and neurodegenerative diseases. Studies have indicated that distinct neurodegenerative diseases can cause infertility, particularly in males, because of hereditary and common molecular pathways. For instance, both neurodegenerative diseases and infertility may be influenced by oxidative stress, hereditary factors, or hormone abnormalities. Neurodegenerative illnesses have the potential to interfere with the hypothalamus-pituitary-gonadal (HPG) axis, which is essential for reproduction. For example, the hypothalamus may be impacted by Parkinson's disease, resulting in hormonal problems that influence fertility. Certain genes like Huntington's disease and dementia may affect reproductive health. These genes have repetition of the trinucleotide sequence (CAG) increases and are common in NDS and Infertility due to mitochondrial malfunction, which stands essential for energy production in gametes and neurons. Oxidative stress, a common cause of chronic inflammation in conditions like Alzheimer's and neurodegenerative diseases, can damage reproductive organs and cause infertility by injuring cells, including germ cells and neurons.

**Keywords:** Neurodegeneration, Infertility, Oxidative stress, HPG axis, Endocrine disruptors.

## INTRODUCTION

**Degenerative diseases and infertility, biological pathways disturbance**

Neurodegenerative conditions such as Parkinson's and Alzheimer's impact gamete viability, sperm and oocyte quality, and neuronal health, resulting in infertility.

Oxidative stress and mitochondrial dysfunction are linked to neurodegenerative diseases such as Alzheimer's disease and Parkinson's disease with infertility, which harm neuronal health and sperm and oocyte quality, showing neurodegeneration and reduced gamete viability (Heimsch et al., 2022). The structure and function of redox-sensitive super-folder (sfroGFP2), a redox biosensor designed to measure oxidizing effects in cells due to its structural stability and raised fluorescence intensity. Amyloid  $\beta$ -peptide ( $A\beta$ ) aggregates extracellularly and induces oxidative stress and inflammation, which is the etiology of Alzheimer's disease (AD) (Fanlo-Ucar et al., 2024). The concept of nitro-oxidative stress, which includes nitric oxide and mitochondrial disturbances, as well as mitochondrial malfunction and biomolecule oxidation. Oxidative stress impacts the reproductive systems of both men and women. Spermatozoal characteristics must be thoroughly assessed for embryonic growth and healthy live delivery. More studies and standardized techniques are needed due to variations in outcomes and different methods for evaluating sperm characteristics (Colaco & Sakkas, 2018). Therefore, oxidative stress plays a role in both genders, although the specific mechanisms and tissues affected may vary. Biosensors and sfroGFP2 can determine structure and fluorescent intensiveness, impacting neural functions and fertility progression, in addition to biomolecule oxidation, mitochondrial dysfunction, and nitric oxide, which affect both men's and women's

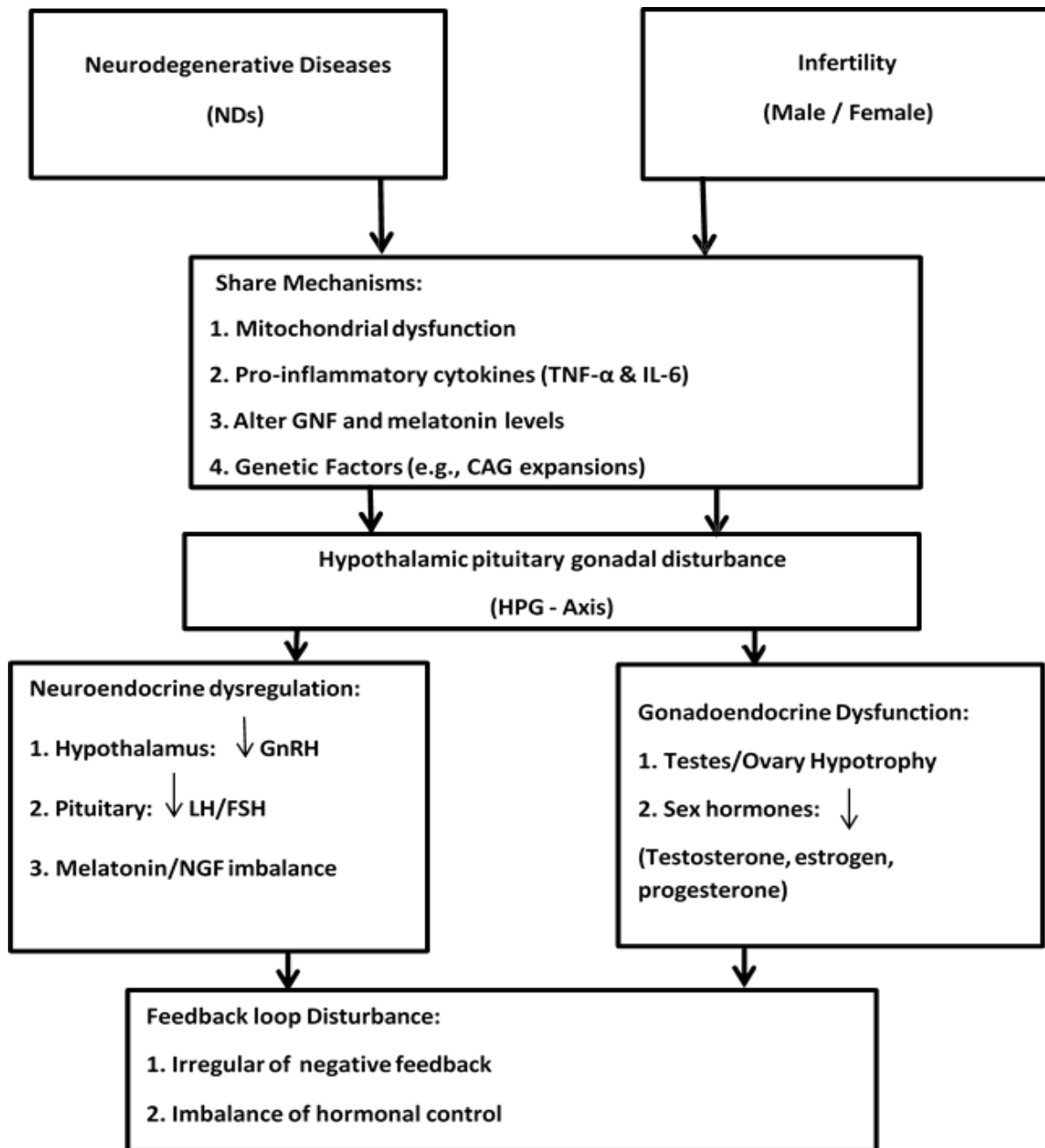
neuroreproductive systems. Mitochondrial dysfunction plays a role in neurological disorders; impaired mitochondria fail to satisfy the heightened energy needs of neurons, ultimately resulting in cellular death. In cases of infertility, especially in males, the propulsion of sperm hinges on mitochondrial ATP (Park & Pang, 2021). When mitochondria are compromised, sperm motility is hindered. In females, the quality of eggs and the progression of embryo development are contingent upon the vitality of mitochondria. Research on mitochondrial failure-related infertility, particularly in males, is limited. Variants impacting the mitochondrial DNA translation pathway cause infertility, and gonadotropin deficit may reverse fertility through ovulation induction treatment (Yildirim & Seli, 2024). POLG (DNA polymerase  $\gamma$ ) is a viable gene candidate for male and female infertility, which is also combined with neurodegenerative diseases. Defects in mitochondrial malformation affect sperm motility, which is a major cause of neurological disturbances in some patients. It also impacts embryo growth and ova quality in females, but it is not well understood. Alterations in the cellular DNA translation pathway can cause infertility, and POLG is a potential gene candidate for both genders. Chronic inflammation, characterized by pro-inflammatory cytokines TNF- $\alpha$  and IL-6, can affect reproductive and neurological tissues, leading to infertility and NDs. Cytokines TNF- $\alpha$  and IL-6 are recognized as inflammatory in free-moving ovariectomized (sterilized) female rats. Lipopolysaccharide (LPS) treatment of the hypothalamic medial preoptic region (MPOA) increased plasma LH, GnRH, IL-1 $\beta$ , IL-6, and TNF- $\alpha$  release while decreasing GnRH and LH production (Watanobe & Hayakawa, 2003; Fraczek & Kurpysz, 2015). IL-1 $\beta$  and TNF- $\alpha$  effectively inhibited the GnRH-LH pathway, while IL-6 did not, so they are the main pro-

inflammatory cytokines involved in LPS-induced reduction of GnRH and LH release. The autonomic nervous system, responsible for male reproductive activities and sexual behavior, controls the spinal cord, spinal nerves, and pelvic floor somatic nerves, impacting fertility and potentially causing infertility (Piekarska et al., 2023). Persistent inflammation is a defining feature of neurological conditions leading to the progression of neurodegeneration. Pregnancy-related bacterial infections can cause fetal growth issues, impacting a child's life. Autism Spectrum Disorder (ASD) therapy can resolve these issues, while serum immune marker profiles of Parkinson's disease predict disease course. In cases of infertility, elevated levels of these cytokines can incite inflammation within the reproductive organs, impacting the implantation process in females and sperm production in males (Yu et al., 2019). Hence, inflammation caused by these cytokines acts as a common denominator, albeit affecting distinct bodily systems.

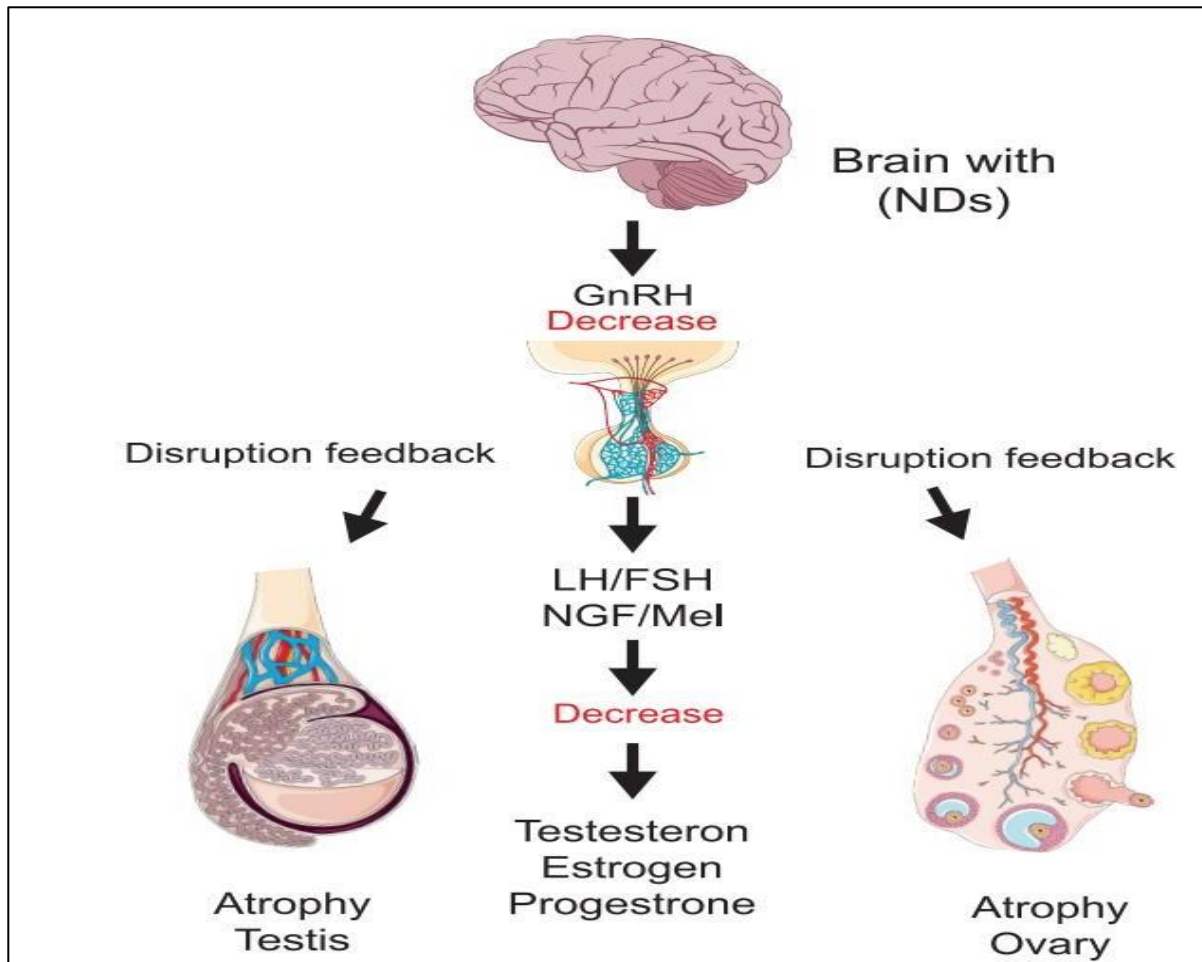
#### **Neurodegenerative diseases and infertility, hormonal disturbance**

The central nervous system depends on sex steroid hormones for learning, cognition, movement, behavior, and reproduction. Sex hormones may also improve synaptic connections, reduce neuroinflammatory processes, and prevent neuronal damage by the activity of metabolizing peripheral steroids in the brain (Vegeto et al., 2020). Hormonal effects on male testes' growth and function, providing androgens and spermatogenesis. Follicle-stimulating hormone (FSH) and testosterone are essential for Sertoli and germ cell proliferation. Research on androgens, FSH, and other hormones is essential for male fertility. Hormonal imbalances can lead to reproductive problems, so understanding molecular pathways and regulatory networks is crucial for developing

effective therapeutic strategies. The Cambridge Baby Development Study investigated maternal insulin resistance, fetal Delta-like noncanonical Notch ligand 1 (DLK1) genotypes, maternal blood DLK1 concentrations, and child size at birth in 613 pregnancies (Santi et al., 2020). The maternal DLK1 concentrations were related to the father-hereditary fetal DLK1 representors (rs12147008) allele, but not the female rs12147008 genotype (Petry et al., 2021). In function and factors influencing the global distribution of the apolipoprotein E (Apo E) gene, single nucleotide polymorphisms (SNPs)  $\epsilon 2$  and  $\epsilon 4$ , which have been associated with long lifespans in centenarians, particularly in connection to cardiovascular and Alzheimer's disorders (Abondio et al., 2019). The Food and Drug Administration and the National Institutes of Health are advocating gender equality in pre-clinical, clinical, and drug development phases to enhance treatment of neurological diseases and save healthcare costs by understanding biological variations between male and female brains. Research on neurological conditions and cognitive impairment in the elderly with neuropathogenic processes in the brain. However, conditions such as faulty spermatogenesis, testicular atrophy, and abnormal HPG axis are becoming more apparent in Huntington's Disease (HD) (Selvaraj et al., 2020). More summarized points also discuss the consequences of studying lifespan in various human populations and its possible adaptive function. Pituitary neurodegeneration interferes with the hypothalamic-pituitary-gonadal (HPG) axis, leading to hypogonadism and infertility, which are often associated with Huntington's or Parkinson's diseases as in Graph 1 and Figure 1. Dysregulation of the HPG axis due to gonadal atrophy and mutant Huntington gene HTT expression, associated with brain cell death, is linked to abnormal neuroplasticity in HD.



**Graph 1.** shows the mechanism and effects of neurodegenerative diseases and infertility on the endocrine system. Hormonal Imbalances, such as Polycystic ovary syndrome (PCOS), stress, and low testosterone (low T) Male hypogonadism disrupt the endocrine system, leading to infertility and neurodegenerative illnesses, altering brain structure, and increasing neurodegeneration risk



**Figure 1.** The pituitary and hypothalamus axis regulates hormonal body homeostasis. Neurological diseases of the brain can affect the pituitary and hypothalamus, causing abnormal hormonal feedback that damages the target endocrine gonads (ovary and testes hypotrophy).

Nerve Growth Factor has been proposed as a potential therapeutic agent for male infertility. It influences the pituitary-gonadal axis and could improve sperm motility and vitality, offering a novel approach to treating infertility related to neurodegenerative diseases. In neurodegenerative illnesses, a loss of nerve growth factor could affect the existence of neurons and their ability to change synaptic relay. When it comes to infertility, NGF's impact is not as referential, yet it may influence the stimulation of reproductive organs and the regulation of hormones. Recent research suggests nerve growth factor may influence

spermatogenesis and testis morphogenesis, potentially preventing gonadal malfunction and improving assisted reproduction outcomes (Ferraguti et al., 2022). It is worth exploring the possible connections between NGF and reproductive functions, possibly in the area of ovarian functionality or testicular well-being. While NGF's role in reproductive processes may not be as prominent as in NDs, its presence is still noteworthy. Hypogonadism is associated with various neurological diseases such as epilepsy, ataxia, demyelination, movement disturbances, and deafness (Alsemari, 2013). Hypogonadism's neurological

conditions may have inherent pathological or physiological causes rather than being thought of as random results, while some antioxidants, such as melatonin, have an opposite rule.

Melatonin, recognized for its anti-inflammatory, anti-excitotoxic, and anti-misfolding properties, has potential neuroprotective functions in ischemia, Alzheimer's, and Parkinson's diseases due to its limited half-life, lack of severe effects, and simplicity of crossing the blood-brain barrier. NDs, like Alzheimer's, can interfere with circadian rhythms and antioxidant defenses, potentially affecting melatonin levels and potentially affecting ovarian and testicular function (Basini & Grasselli, 2024). Alzheimer's disease (AD) can disrupt circadian rhythms and antioxidant defenses, potentially affecting melatonin levels and gonadal function.

In neurological disorders, diminished levels of melatonin result in reduced resistance against oxidative stress and disturbances in sleep patterns, which additionally worsen symptoms. Within the field of infertility, melatonin plays a significant role in influencing reproductive hormones; decreased levels may disrupt both menstrual cycles and ovulation. Melatonin supplementation improved oocyte quality and intrauterine oxidative regulation in patients, resulting in a high rate of pregnancies. Clinical studies are required to confirm the effectiveness of melatonin, despite indoleamine's potential therapeutic effects (Espino et al., 2019). Furthermore, due to its antioxidant properties, a decrease in melatonin could potentially contribute to oxidative stress within reproductive tissues. Hence, while both conditions are influenced by melatonin levels, the mechanisms through which they are affected diverge significantly.

### **Degenerative diseases and infertility, genetic overlapping**

Expansions of CAG gene, trinucleotide repetitions in genes like HTT (Huntington's disease) and AR (androgen receptor, related to male infertility), are linked with neurodegeneration and reproductive dysfunction (Reshi et al., 2022). Huntington's disease is triggered by CAG repeats in the HTT gene, with those with Parkinson's, Alzheimer's, and frontotemporal lobar dementia having intermediate variants more frequently, potentially leading to AD pathophysiology (Menéndez-González et al., 2019). An instance of a neurodegenerative disease in which CAG repeats in the HTT gene trigger protein misfolding is Huntington's disease. Concerning infertility, the relationship is less specific. However, certain patients with male infertility are associated with CAG expansions in the androgen receptor gene, leading to delays in spermatogenesis. The CAGn locus, found in 286 Russian infertile men, is associated with male infertility and spinal and bulbar muscle atrophy, with 97% of mutations having 16-29 repeat variants (Chernykh et al., 2024). Thus, while CAG expansions are traditionally more correlated with NDs, a connection to infertility exists, albeit less frequently observed.

Kennedy syndrome is linked with CAG repeat expansions in the androgen receptor gene. This male infertility arises from genetic change related to compromised spermatogenesis characterized by conditions such as oligozoospermia or azoospermia (Müller et al., 2022).

The APOE4 gene variant, a risk factor for Alzheimer's disease, may result in infertility in women due to changes in lipid metabolism (Darabi et al., 2024). The expansion of these repeats genes not only affects fertility in male

and female but also contributes to the progression of neurodegenerative diseases. In contrast, genetically inherited neurodegenerative disorders combined with hormonal and genetic problems cause infertility (Yu et al.2019). Infertility is caused by

multiple sclerosis and oxidative stress and inflammation in the uterus, whereas neurological problems are influenced by hormonal variables such as estrogen, as in Table 1.

**Table 1.** Infertility is associated with neurodegenerative diseases, which disrupt the nervous and endocrine systems, oxidative stress, metabolism, and reproduction. Anomalies in the HPG axis affect reproductive hormone levels, causing infertility.

Scientific Point	Neurodegenerative Diseases	Infertility
<b>Oxidative Stress</b>	Damages neurons, leading to cell death and neurodegeneration (e.g., Alzheimer's, Parkinson's, Huntington's).	Impairs sperm and oocyte quality, leading to DNA damage, poor fertilization, and pregnancy complications.
<b>Mitochondrial Dysfunction</b>	Contributes to neuronal energy deficits, increased ROS, and apoptosis, exacerbating disease progression.	Defects in sperm and oocytes reduce fertility potential, affect embryo development, and contribute to reproductive aging.
<b>Cytokines (TNF-α &amp; IL-6)</b>	High TNF-α and IL-6 promote neuroinflammation, neuronal apoptosis, and blood-brain barrier breakdown in conditions like Alzheimer's and multiple sclerosis.	High TNF-α and IL-6 levels are linked to endometriosis, polycystic ovary syndrome (PCOS), and sperm dysfunction, reducing fertility.
<b>Nerve Growth Factor</b>	Altered decrease in NGF levels are observed in neurodegenerative conditions.	NGF dysregulation can impair fertility by decreasing folliculogenesis, and sperm maturation .
<b>Melatonin Levels</b>	Low melatonin leads to increased oxidative stress and neurodegeneration, worsening conditions like Parkinson's and Alzheimer's disease.	Low melatonin disrupts circadian rhythms, reduces oocyte and sperm quality, and affects reproductive hormone regulation.
<b>CAG Expansions</b>	CAG trinucleotide repeat expansions in genes like <i>HTT</i> (Huntington's disease) cause toxic protein aggregation and neurodegeneration.	CAG expansions in genes like <i>AR</i> (Androgen Receptor, linked to Kennedy's disease) can impair spermatogenesis and lead to infertility.

### **Degenerative diseases and infertility, environmental factors**

Lifestyle decisions, environmental factors, stress, lack of exercise, nutrition, obesity, smoking, and alcohol use can impact brain health and fertility. Long-term exposure to toxic chemicals raises the risk of infertility and NDs, which are linked to endocrine disruptors like pesticides and chemicals like bisphenol A (BPA), which interact with hormones and cause neurotoxicity. BPA, an environmental endocrine disruptor, can impair cognition by modifying neurite outgrowth and raising HDAC2 expression (Bi et al., 2022). BPA exposure, related to female infertility, impacts peak estradiol levels, recovered oocytes, post-reproductive treatments, premature maturation, and BPA-related disorders, according to experimental studies (Pivonello et al., 2020). The neurotoxicity of pesticides, herbicides, and fungicides on humans and animals has confirmed a connection between exposure and neurological disorders in people (Richardson et al., 2019). Pesticides such as carbamates, pyrethrins, pyrethroids, organophosphates, and organochlorines are causing significant human exposure, reproductive issues, and infertility disorders (Reshi et al., 2022). Understanding and regulating reproductive toxicity mechanisms is essential to mitigate possible hazards.

DNA integrity is essential for conception, pregnancy, and childbirth, while damage can trigger infertility. Aging, radiation, and chemotherapy can cause oocyte DNA damage, leading to the link between infertility and DNA damage (Xu et al., 2024). Neurons, due to their high energy needs and long lifespan, are exposed to DNA damage, leading to neurodegenerative disorders. Understanding the link between DNA damage and dementia, particularly decline in aging brains, is crucial

(Welch & Tsai, 2022). DNA repair is crucial for cognitive function and healthy aging, but mutations can cause disorders like ataxia-telangiectasia, Werner syndrome, Cockayne syndrome, and xeroderma pigmentosum group A, leading to neurodegeneration (Wang et al., 2021). As maternal and paternal chronological age increases, the possibility of NDs and infertility increases due to common events like DNA damage accumulation.

### **Neurodegenerative disease and infertility, clinical observations**

Men with Parkinson's disease often experience hypogonadism and erectile dysfunction due to dopaminergic and hypothalamic dysfunction. About 41% of males had functional hypogonadism, 13% had organic hypogonadism, and 46% were gonadal, with hypogonadal males having lower International Index of Erectile Function-5 (IIEF-5) scores and higher Clomiphene Citrate Index (CCI) (Lisco et al., 2023). Serum fertility test (FT), Sex Hormone Binding Globulin (SHBG) and CCI are crucial indicators of Erectile Dysfunction (ED) severity, with middle-aged or older individuals more likely to have severe Neural tube defects (NTDs), necessitating appropriate clinical procedures and treatments. Women who have Alzheimer's disease (AD) that develops early have a lower ovarian reserve. The impact of estrogens and Apolipoprotein E (APOE) genotype on women's Alzheimer's condition precocity, emphasizing the significance of considering sex-specific risk aspects in hormone therapy and menopause (Valencia-Olvera et al., 2023). Studies indicate menopause-related E2 depletion, APOE genotype, female sex, and hormonal therapy (HT) are linked to cognitive reduction and Alzheimer's disease, needing more investigation for precision medicine.

### Neurodegenerative disease and infertility, specific insights

Neurological disorders causing motor difficulties, cognitive impairment, and behavioral and personality disorders, allowing patients at risk to make informed decisions. Reproductive testing aids in dealing with Huntington's disease, a neurological disorder causing motor difficulties, cognitive impairment, and behavioral and personality disorders, allowing patients at risk to make informed decisions (Reshi et al., 2022). The reviewed literature on reproductive options and HD risk focuses on real reproduction, assistance choices, decision-making challenges, and the connection between HD genetic risk and procreation desire (Fahy et al., 2023). The study highlighted the significance of using helpful options in decision-making and reproductive outcomes and the development of a high-definition reproductive decision model. The studies' quality varied, and it was challenging and emotionally exhausting to make reproductive rulings in HD risk circumstances.

A molecular connection between male infertility and Purkinje cell degeneration (pcd), suggesting comparable pathways may be present in both conditions. A rat mutant with cerebellar ataxia was the first to demonstrate pcd, affecting cerebellar Purkinje cells (PCs), retinal photoreceptors, mitral cells, and thalamic neurons (Zhou et al., 2018). Mutations in the *Nna1* gene, which are liable for Purkinje cell degeneration, also result in spermatogenesis.

The neurodegenerative disease identified as Niemann-Pick Type C1 (NPC1) disease is the cause of infertility. Heterozygotes with NPC1 mutations show diverse biological differences, potentially rare for autosomal recessive illness

of cellular lysosomes. Specifically, NPC2 deficiency significantly affects fertility (Erickson, 2018). Lysosomes are crucial intracellular organelles for apoptosis, autophagy, exocytosis, and endocytosis, and their activity is vital in the female sex hormones, promoting ovarian preparation, uterine secretion, and early pregnancy (Li et al., 2020). In *Drosophila*, infertile deficiency can partially fix spermatogenesis deficiencies caused by NPC1 mutations, further connecting sterol metabolism to both neurodegeneration and infertility that may be caused by identical metabolic or genetic causes (e.g., *PSEN1* gene mutations). Rat experiments demonstrate that expressing the *Npc1* protein in glial cells can cure infertility, indicating the significance of restoring hypothalamic control over the pituitary for fertility and emphasizing the need for further investigation.

Neurodegenerative diseases and infertility, current consensus and challenges Epidemiological and mechanistic investigations of neurodegenerative diseases and infertility share similarities, but causation remains unclear due to misunderstandings, leaving it uncertain whether neurodegeneration precedes infertility or vice versa. The complexities of NDs and infertility complicate straightforward connections between factors such as hereditary malformation. Human ethics studies have observational limitations, and experimental models (such as transgenic mice) might not precisely imitate humans. Neurodegenerative diseases and infertility can be effectively managed using assisted reproductive technologies like intracytoplasmic sperm and surgical sperm retrieval and injection, which assist patients with neurological diseases to overcome ejaculation issues and poor semen properties.

### Conclusion

There are common pathways that correlate neurodegenerative diseases and infertility, including oxidative damage, hormone imbalance, and genetics. To demonstrate causation, however, extensive longitudinal studies are necessary. Recognizing these

associations may contribute to enhanced diagnostic and therapeutic strategies, and clinicians managing NDs patients should incorporate reproductive health assessments in inclination.

**Declaration of Interests:** The authors have no conflict of interest to declare.

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