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REVIEW ARTICLE

The Role of Stress in the Progression of Motor Neuron Disease: Mechanisms and Implications for Treatment

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KEYWORDS

environmental factors, stress, MND, HPA, microglia, oxidative stress

ABSTRACT

Motor neuron diseases (MND) are a group of rare neurodegenerative diseases that significantly affect the survival of patients. The disease progresses rapidly, and currently, there is no cure for MND. Therefore, delays in MND progression and improvements in the patient's quality of life have become crucial aspects of clinical work. Stress—a response to environmental or psychological changes—significantly affects body metabolism. In particular, excessive stress can harm the human body. Here, we review recent literature exploring the impact of stress on the progression of MND. This review also discusses the potential mechanisms of stress-induced MND deterioration, including activation of the hypothalamic–pituitary–adrenal axis, abnormal microglial activation, oxidative stress, and the accumulation of stress granules. The role of stress in the pathological changes of MND and the importance of stress management in the treatment of MND have been emphasized. Here, we highlight that the attention of clinicians to this crucial aspect can significantly influence the course and outcome of the disease.

1 Introduction

Motor Neuron Diseases (MNDs) represent a group of rare neurodegenerative diseases that result from degeneration of the upper and lower motor neurons in the central nervous system (CNS). Their degeneration leads to the dysfunction of controlled skeletal muscles, affecting activities such as walking, breathing, speaking, and swallowing [1]. MNDs encompass several types of diseases, including amyotrophic lateral sclerosis (ALS), progressive bulbar palsy, primary lateral sclerosis, progressive muscular atrophy, spinal muscular atrophy, Kennedy's disease, and postpolio syndrome. Among these, ALS is the most prevalent form of MND [2]. Typically, individuals with MND experience a gradual onset of muscle weakness, which eventually leads to disability. However, it is important to note that a subset of MND patients may exhibit a rapidly progressive course. The underlying reasons for this accelerated progression in some patients remain unknown [3]. Accumulating evidence indicates that environmental stress may contribute

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to the accelerated progression of MND [4]. Several mechanisms, including genetic factors, blood-brain barrier (BBB) disruption, mitochondrial dysfunction, excessive (oxidative and nitric oxide) free radical production, and tau protein accumulation, have been proposed to contribute to the progression of MND [5–7].

Stress responses in humans help them adapt to new environments by triggering the "fight or flight" response and regulating various metabolic and immune processes [8, 9]. However, excessive environmental stress stimuli can often lead to psychological symptoms such as anxiety, fear, and depression. Additionally, it can result in physiological fatigue and various forms of discomfort [10]. Thus, long-term chronic stress or short-term intense stress can aggravate factors contributing to the development of certain diseases or exacerbate the progression of existing conditions [10]. Chronic and uncontrolled stress is usually associated with the occurrence and development of cardiovascular, mental, and neurodegenerative diseases, especially in individuals who are susceptible to stress [11, 12]. The current treatment options for MND are limited. There is an urgent need for further research and understanding of the pathophysiological mechanisms underlying disease progression. This knowledge will be crucial for identifying and developing more effective therapeutic strategies for MND. This review explores the role of stress in the progression of MND and discusses the potential mechanisms and implications for treatment.

2 The epidemiology of MND

MND is a rare condition, with an incidence rate of 1-2 per 100,000 individuals and a prevalence of 4-6 per 1 million people in most parts of the world, excluding the Western Pacific region [13, 14]. MND occurrence increases with age, reaching a maximum between the ages of 40 and 70 years, and is more prevalent in men than in women [4, 15]. For instance, a study conducted on the UK population revealed that the prevalence of MND was about 2.6 per 100,000 women and 3.9 per 100,000 men per year [16]. The limited number of studies and statistics available for nonEuropean populations indicate that the prevalence of MND in Asian populations is <1/100,000 [17]. The factors contributing to the regional disparities in MND prevalence remain inadequately understood.

The etiology of MND encompasses a range of genetic and environmental factors. In the past three decades, there have been many studies on the genetic correlation with MND. Mutations in several genes (SOD1, TARDBP, FUS, OPTN, and C9orf72) are closely associated with MND, with 20% of familial cases carrying SOD1 mutations [18]. C9orf72 mutations were found in 30-50% of familial cases [19, 20]. TARDBP and FUS mutations were found in approximately 10% of familial cases [21–23]. However, for sporadic cases, except for C9orf72 and SOD1 mutations found in 10% and 2% of cases, other related genes account for <1% of the cases [24]. Therefore, environmental factors play a significant role in the majority of sporadic cases.

2.1 The epidemiology study of the relationship between stress and MND

Numerous studies have demonstrated that professional athletes who participate in adversarial ball games have an increased risk of MND [25–27]. Compared to the general population, athletes tend to experience trauma and stress at a higher rate, suggesting that stress has a significant impact on the prevalence of MND. However, these studies did not elucidate the history of trauma or stress [25–27]. Several meta-analyses have underscored the correlation between MND and stress caused by trauma, particularly head trauma. However, a clear causal

relationship between the two has not been definitively established [28, 29]. Thus far, it can be confirmed that stress significantly affects the prevalence of MND. The exact nature of this relationship, particularly in the context of trauma history, remains unclear.

3 Symptoms and signs of MND

MND is a group of neurodegenerative diseases, including ALS, progressive muscular atrophy, primary lateral sclerosis, and progressive medulla palsy. The most common type of MND is ALS [2]. Its pathological features include progressive weakening of the medulla oblongata, limbs, and respiratory muscles caused by progressive degeneration of the upper motor neurons and lower motor neurons, as well as relative weakening of the ocular muscle and sphincter function [30]. MND typically starts with mild, localized muscle spasms or weakness, which gradually progresses to the paralysis of nearly all skeletal muscles without any sensory impairment. Approximately 60% of the initial symptoms manifest as local limb weakness, while 30% present with dysarthria, which is caused by abnormal functioning of the medulla oblongata. Frontotemporal dementia (FTD) and respiratory myasthenia each account for approximately 5% of the onset symptoms [15].

4 Pathogenesis of MND

In patients with MND, degeneration of motor neurons occurs in the motor cortex of the brain, the motor nucleus of the brain stem, and the anterior horn of the spinal cord. This deterioration of motor neurons leads to atrophy of the target muscles. As MND progresses, inclusion bodies can be detected in affected spinal motor neurons [31]. The ubiquitinated protein TDP-43, encoded by the gene *TARDBP*, is an inclusion body marker in the majority of MND cases. A limited number of C9orf72 mutant cases were TDP-43 positive; however, their inclusion bodies contained abnormally translated dipeptide repeats derived from unusual hexanucleotide repeats [19]. In SOD-1/FUS-associated MND cases, TDP-43 was replaced by abnormal aggregation and ubiquitination of SOD-1 and FUS. These gene mutations commonly cause RNA metabolism dysregulation, which is strongly associated with tau protein aggregation [19, 32–34]. Although it is not clear whether the immune system plays a major role in the pathogenesis, patients with autoimmune diseases are certainly more likely to suffer from MND [35]. Other significant mechanisms causing MND include BBB destruction, mitochondrial dysfunction, excessive production of oxidation and nitric oxide free radicals, and tau protein accumulation [5–7].

5 Stress impacts the progress of MND

The origin and manifestation of stress can differ significantly. The level of oxidative stress in people with mental illness is generally higher than that in normal people [36]. Unhealthy lifestyle habits, such as smoking, drinking, and high BMI, can exacerbate the body's stress level [37–39]. Furthermore, apart from the persistent environmental factors discussed above, the history of toxic exposure, trauma, and other harmful adverse events inevitably puts the body in a state of acute stress. Trauma, particularly brain trauma, exacerbates the progression of MND in animal models [40]. Adverse events, such as prior exposure to heavy metals (including lead), pesticides, physical trauma/injury, electric shock history, and prior exposure to organic solvents, are significantly associated with the progression of MND and serve as risk factors for MND [3]. A study of the New Zealand population revealed that cranial trauma, prolonged strenuous exercise, and emotional trauma (particularly in patients

with chronic mental stimulation) can cause MND to progress faster compared with the general population, which experienced none of the above [41]. Interestingly, certain psychological interventions can significantly improve the quality of life for MND patients [42, 43]. Extreme high-temperature weather (including that caused by global warming) also affects the disease course of MND patients through heat stress [44].

Evidence that stress, whatever its form, affects MND progression is solid. Therefore, it is necessary to review the available literature on the relevant stress-mediated mechanisms involved in the progression of MND. It is crucial to improve stress response interventions and the prognosis for MND patients.

6 Possible mechanisms related to stress in MND

6.1 Stress-induced hypothalamic–pituitary–adrenal (HPA) axis activation in MND

A key physiological system closely related to stress is the hypothalamic–pituitary–adrenal axis (HPA). Under stress, the activated HPA axis releases glucocorticoids (GC) and mineralocorticoids (MC) [45]. GCs traverse the BBB to activate the glucocorticoid receptor (GR) and mineralocorticoid receptor (MR). Activation of these two receptors is an important means of coping with stress in the brain. Within the CNS, GR is widely expressed in neurons, microglia, monocytes, astrocytes, and oligodendrocytes, whereas MR is selectively expressed only in microglia and astrocytes [46]. During an acute stress response, GC signals ensure strict regulation of the HPA axis through MR and GR, which enables the body to adapt physiologically and behaviorally to environmental factors by integrating and coordinating central nervous endocrine pathways [47]. However, under uncontrolled or long-term psychological stress, these adaptive changes prove insufficient to cope with changes in environmental factors. Failure of negative feedback may result in GC signal dysregulation, leading to overactivation of the HPA [48–50]. Chronic HPA axis activation affects microglial function, consequently elevating the susceptibility to neurodegeneration and increasing the risk of neuronal degeneration in the brain [51]. The abnormal activation of microglia has been observed in various psychiatric disorders, including anxiety, depression, schizophrenia, and autism spectrum disorders. Patients with related diseases are trapped in a state of chronic stress for extended periods [52–55]. Overactivation of the HPA axis activates microglia, resulting in the release of inflammatory cytokines and autoimmune and BBB disorders, among other mechanisms, which affect the function of neurons and the homeostasis of the internal environment. In stressed mouse models, HPA axis overactivation causes neuroinflammation, which in turn promotes motor neuron injury [56]. Long-term elevated GC also marks the onset of pathological tau protein accumulation [57].

The increase in GC levels during stress causes an increase in blood glucose levels. However, the relationship between hyperglycemia and MND remains unclear. Studies on diabetes and MND may provide insights into the impact of hyperglycemia on MND. The available research on diabetes and MND is conflicting [58]. A study conducted in the Caucasian population showed that individuals with diabetes had a lower risk of MND and a delayed onset time compared with those without diabetes [59]. Subsequent studies also suggested that diabetes serves as a protective factor against the onset of MND [60, 61]. Two studies conducted in Asian populations also yielded similar results [62, 63]. They found that the average onset time of MND was delayed in patients with type 2 diabetes,

especially in patients over 55 years of age [63]. However, two case-control studies conducted in the Nordic population revealed that patients diagnosed with diabetes before the age of 40 years had an increased risk of MND, whereas those diagnosed with diabetes after the age of 40 years had a decreased risk of MND [60, 64]. Another study highlighted that patients with diabetes are at a significantly increased risk of developing ALS, with an overall hazard ratio (HR) of 1.35 as compared to nondiabetic patients [65]. A Mendelian randomization study revealed that while the HR of young men with diabetes (<65 years old) increased, the trend for the risk of ALS among elderly men with diabetes and women (>65 years old) remained constant, albeit not significant [66]. In conclusion, diabetes or hyperglycemia may be risk factors for MND in young patients. Diabetes may protect against MND in elderly Caucasians, whereas it increases the risk in Asians. The population and regional differences in clinical characteristics, potential molecular mechanisms, and genetics may potentially explain these contradictory findings [66, 67].

6.2 Stress-mediated microglia activation and inflammatory response injurious to neurons

Neuroinflammatory responses have been observed in patients with both familial and sporadic MND. The occurrence of neuroinflammation is closely related to microglia activation [68]. Brain tissues exposed to psychological stress exhibit elevated levels of inflammatory cytokines, abnormal activation of microglia, and aggregation of peripheral macrophages and monocytes [69]. Studies on schizophrenia, depression, suicidal tendencies, and posttraumatic stress disorder have revealed that these patients exhibit dysregulation of major inflammatory cytokines, particularly IL-6, IL-1β, IL-18, and C-reactive protein [70–74]. In conclusion, the relationship between stress and neuroinflammation remains indisputable.

As previously stated, microglia are controlled by the HPA axis because they express GC receptors. Under acute stress, the innate immune system of the CNS releases high mobility group box-1 (HMGB-1), a danger signal that interacts with the NLRP3 inflammasome to stimulate microglia [75]. In addition to HMGB-1, heat shock protein 72 (Hsp72) and ATP, released during stress, trigger an inflammatory-immune response [75, 76]. Microglia activation recruits peripheral immune cells to enter the CNS and produce inflammatory cytokines [77]. Inflammasome activation is frequently observed following stress [78]. Danger signals (HMGB-1, Hsp72, ATP, etc.) activate inflammasomes via toll-like receptors (TLRs) and induce the release of inflammatory cytokines from inflammatory cells. Among them, HMGB1 and Hsp72 are endogenous ligands of TLR and are related to the NF-κB signaling pathway. NF-κB is a significant inflammatory signaling pathway that facilitates the transcription and translation of inflammatory mediators, including IL-1B, IL-18, IL-6, and TNF-α [76]. Figure 1 illustrates the mechanism by which stress causes the elevation of related inflammatory mediators.

As the number of macrophages and peripheral monocytes in the CNS increases, the levels of inflammatory factors (IL-1β, IL-18, TNFα, and IL-6) in the brain continue to rise, ultimately resulting in the inflammatory damage of neuronal cells [79].

MND progression is amplified by the inflammatory response of activated CNS microglia, peripheral lymphocytes, and macrophages [80]. Therefore, the inflammatory-immune cascade induced by stress intensifies the progression of MND. As mentioned above, danger signals (being endogenous ligands of TLR) activate NF-κβ-related signaling pathways, which not only mediate the transcription and translation of

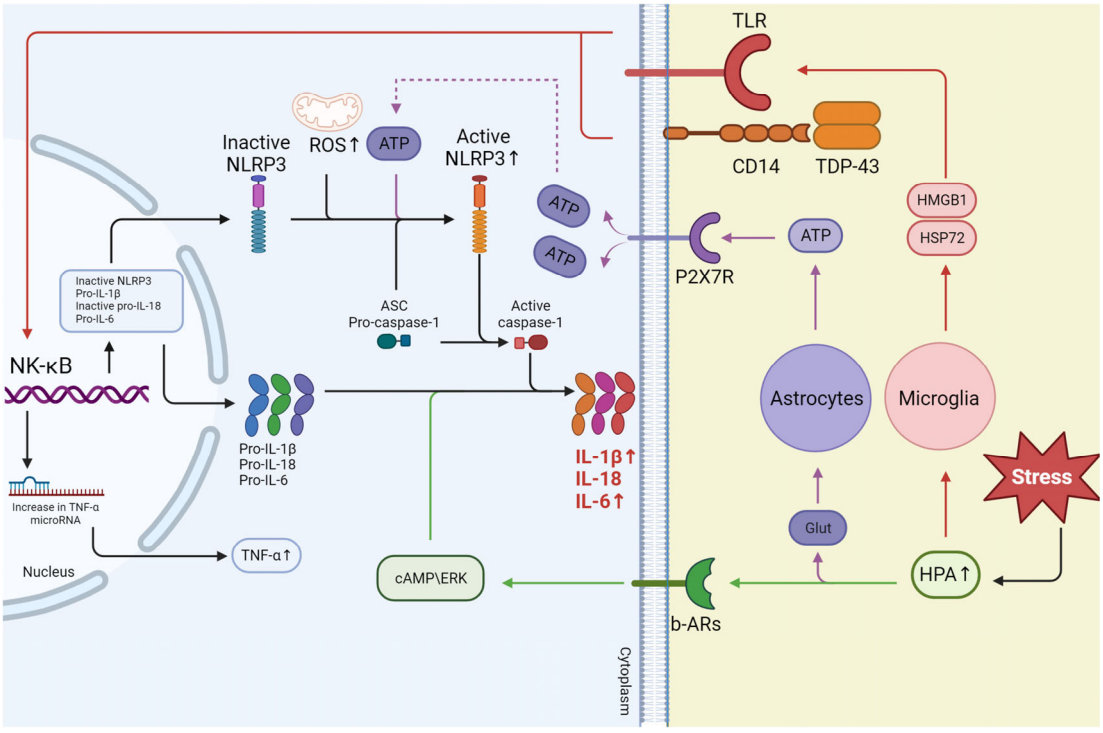


Figure 1 Stress-induced the activation of neuroimmune cells and the release of inflammatory mediators

Stress upregulates the HPA axis and stimulates microglia to secrete danger signals (such as HMGB1 and HSP72), thus acting on TLR to activate the NK-κB pathway. In addition, TDP-43 also participates in the activation of NK-κB in combination with CD14. NK-κB pathway activation upregulates TNF-α secretion, and consequently, inactive NLRP3, pro-IL-18, pro-IL-1β, and pro-IL-6 are produced. NLRP3 is activated by ROS and ATP derived from activated astrocytes. Active NLRP3 trims ASC pro-caspase-1 into active caspase-1. Active caspase-1 transforms pro-inflammatory cytokines into inflammatory cytokines. In addition, the activation of the cAMP\ERK pathway by b-ARs also induces the production of related inflammatory cytokines after HPA axis activation.

inflammatory mediators IL-1β, IL-18, IL-6, and TNF-α but also induce the secretion of reactive oxygen species (ROS), thus causing oxidative damage. The relevant mechanisms will be detailed in the following section on oxidative stress damage [81].

6.3 Stress Granules (SGs) assembly during chronic stress could damage neurons

SGs are assemblies of untranslated messenger ribonucleoproteins (mRNPs) formed from mRNA that have stalled at the initiation stage of translation [82]. Formed under stress conditions, SGs can act as signal centers that regulate the adaptive physiological responses of cells to stress [83]. SGs enhance cell survival during adverse stress by regulating protein translation and material transport and sometimes by regulating apoptosis [83–85]. RACK1 (receptor for activated C kinase 1), a regulator of apoptosis, is recruited and chelated by SGs during stress. SGs block the interaction between RACK1 and mitogen-activated protein 3 kinase 4 (MAP3K4), thus inhibiting the Rack1-mediated apoptosis pathway [86]. Moreover, SGs can inhibit apoptosis by recruiting the regulatory protein mTOR to block overactivation of the mTOR complex 1 (mTORC1) signaling pathway [83]. In addition to regulating RACK1 and mTOR, SGs regulate cell signaling pathways by isolating proteins such as tumor necrosis factor (TNF) receptor-associated factor 2 (TRAF2) [87]. Under stress, SGs can segregate proteins associated with mRNA physiology and metabolism, resulting in the temporary inhibition of translation and the prevention of misfolded protein accumulation [88].

Normally, SG components exist as "free form" molecules or oligomers in their original state. The biophysical process known as liquid-liquid phase separation (LLPS) drives the formation of droplet-like cell structures from the free form SGs components [89]. Interactions that contribute to SG formation include traditional LLPS protein-protein and protein internally disordered regions(IDRs) interactions [90]. The Ras-GAP Sh3-binding protein (G3BP) family plays a crucial role in the initiation of SG assembly. Two members of the G3BP family, G3BP1 and G3BP2, are indispensable starter components for SG. The expression of G3BP1 and G3BP2 is essential for the assembly of SG, and they drive the assembly of SGs by employing the LLPS mechanism [91]. G3BP1 and G3BP2 have similar sequences and biophysical properties. Furthermore, G3BP1 is a central node of the LLPS mechanism. Thus, our attention was primarily drawn to G3BP1. G3BP1 regulates LLPS through dimerization and the net charge distribution in distinct domains [92]. G3BP1 contains three internally disordered regions (IDRs): IDR1 carries a net negative charge, and IDR2 and IDR3 carry a net positive charge. RNA-binding domains (RBD) and NTF2-like domains are also present in G3BP1. The NTF2-like domain mediates G3BP1 dimerization, which supports the LLPS mediating role of G3BP1 and thus helps SG assembly [92, 93]. G3BP1 S149 phosphorylation crucially regulates SG assembly. It ultimately negatively regulates LLPS and the formation of SG by increasing the negative charge density of IDR1, enhancing the interaction between IDR1 and (positively charged) IDR3, shielding RBD, and reducing the G3BP1-RNA-binding strength [92]. Thus, G3BP1 S149 dephosphorylation is necessary to initiate SG formation, whereas IDR1 acts as a conformational switch that controls RNA binding and the subsequent assembly of SGs in cells. Cellular stress causes G3BP1 S149 phosphorylation and leads to the release of free mRNA from polyribosomes [94]. The addition TDP-43/FUS/hnRNPA1, a classic SG member, can be recruited by GBP condensates. Genetic mutations lead to structural and functional abnormalities in SGs [93]. Interestingly, G3BP1 (the main trigger initiating SG assembly) also plays an important role in SG clearance. The K-63-linked ubiquitination in the N-terminal NTF2-like domain of G3BP1 promotes G3BP1-VCP interaction, targeting G3BP1 to the endoplasmic reticulum Vcp-FAF2 complex for degradation [95].

In addition to G3BP, ubiquitin-associated protein-2-like (UBAP2L) also plays a pivotal role in regulating SG formation [96]. When cells are stressed, UBAP2L-positive droplets are the first to appear in the cytoplasm, followed by G3BP1 recruitment and clocalization [97]. Furthermore, in most cases, the knockout of UBAP2L severely reduced the assembly efficiency of SGs [97]. The Arg–Gly–Gly (RGG) motif of UBAP2L is necessary for recruiting other SG components; RGG and G3BP physically interact. Acute stress reduces UBAP2L methylation, which is controlled by the arginine methyltransferase PRMT1 on RGG. Reduced methylation enhances the strength of UBAP2L interactions with SG components (such as G3BP) [98].

The reduction in the antiinterference ability of SG assembly is likely modulated by various factors that regulate the assembly dynamics of SGs. Cellular dysfunction and cell death are associated with impaired assembly dynamics of SGs under chronic stress [99]. SG dysfunction is turning out to be an important pathological mechanism in several neurodegenerative diseases. To date, studies have shown that SGs are closely associated with many neurodegenerative diseases, including MND, AD, and MS [100]. In these diseases, misassembled or unbroken SGs are

associated with disrupted RNA metabolism and the accumulation of aggregates that lead to neuronal death [99].

In conclusion, chronic stress damages neurons by affecting the assembly and function of SGs, a crucial factor in the emergence and progression of MND. Moreover, autophagy dysfunction leads to a lack of SG degradation, which assumes a crucial function, particularly during chronic oxidative stress [101]. p62 is an autophagic cargo receptor. Chronic oxidative stress leads to a significant accumulation of p62 in the cytoplasm, which is largely colocalized with SGs. Autophagy disorders caused by oxidative stress affect SG clearance, leading to its pathological accumulation in the cytoplasm [101]. The VCP complex plays an extensive role in SG clearance [95]. In animal models, dysfunctional VCP complexes significantly hindered the breakdown of SG, resulting in elevated levels of cellular oxidative stress [102]. As discussed later, oxidative stress has an array of adverse effects on cells.

Chronic stress can perpetuate pathological SGs, giving rise to a range of abnormal pathological activities such as long-term inhibition of protein biogenesis and abnormal cytoplasmic protein fibrosis [103, 104]. This results in various neuropathological symptoms, including MND [105–107]. In MND, chronic or intense stress-mediated SG dysfunction may also cause the inclusion bodies to contain tau protein [108]. However, the exact mechanism by which SG affects MND requires further investigation.

6.4 Chronic stress-mediated abnormal cytoplasmic accumulation of TDP-43 is neurotoxic

Abnormal accumulation of TDP-43 in the cytoplasm is observed in most cases of MND. As a member of the SG family, TDP-43 is a classical RNA-binding protein associated with MND. It can shuttle between the cytoplasm and the nucleus. TDP-43 is a key component of neuronal ubiquitin-positive inclusions, a pathological marker of MND [109]. TDP-43 regulates RNA metabolism, protein translation, mitochondrial autophagy, axon transport, vesicular transport, and stress response. Its structure consists of an N-terminal domain (NTD, 1-102aa), two RNA-recognition motifs (RRM1, 106-177aa, and RRM2, 192259aa), and a C-terminal domain (CTD/PrLD, 274-414aa) [110]. Under normal stress, TDP-43 is physically and chemically separated from the cellular environment by LLPS through PrLD regulation. It aggregates and fuses into gelatinous membrane-less organelles and then uses active transport and passive diffusion to enter the cytoplasm[111, 112]. In the cytoplasm, the RRM structure of TDP-43 binds to RNA and other SG components to form SGs. These SGs regulate mitochondrial function to prevent cellular damage inflicted by stress-induced inflammatory factors. This process suppresses cellular damage caused by inflammatory stress [110, 111, 113]. At the end of the stress stimulus, nuclear localization signals (NLS, 82-98aa) bind to nuclear input receptors and guide TDP-43 back into the nucleus, coassisted by the Ras-associated nuclear (RAN) GTPase activation protein [114].

The nuclear absence of TDP-43 and cytoplasmic accumulation of hyperphosphorylated, ubiquitinated, and cleaved TDP-43 are pathological hallmarks of MND [115]. Under conditions of chronic or oxidative stress, TDP-43 is phosphorylated to pTDP-43 in the cytoplasm, where it aggregates abnormally. Chronic oxidative stress can lead to mitochondrial autophagy dysfunction, and the abnormal accumulation of pTDP-43/SGs products cannot help mitochondria cope with oxidative damage. Therefore, pTDP-43/SGs inclusion bodies cannot be eliminated [101, 113]. Abnormal accumulation of pTDP-43/SGs in the cytoplasm results in the production of many dysfunctional gene products, most of which

are mitochondrial proteins encoded by the nuclear genome. They also cause mitochondrial dysfunction, which exacerbates oxidative stress in cells. This stress-aggregation cycle is one of the foundations of the occurrence and development of MND [116]. In addition, cytoplasmic pTDP-43 liquid droplets slowly recruit Importin-a (a nuclear import transporter) and Nup62 (a nuclear pore component) under chronic stress, inducing mislocalization of RanGap1, Ran, and Nup107 (a nuclear pore component). RanGap1 is required for RAN-dependent nuclear input and output. Therefore, TDP-43 is inhibited from translocating into the nucleus [101, 117].

MND is characterized by the formation of cytoplasmic TDP-43 inclusion bodies, accompanied by the absence of normal TDP-43 in the nucleus [118]. Abnormal intracellular aggregation of TDP-43 can induce toxicity, leading to neural and axonal damage [119]. TDP-43 becomes dysfunctional, and as a result, the nucleus gradually loses TDP-43, ultimately resulting in cell death [101, 117]. The nuclear transport of TDP-43 under three different conditions is highlighted in Figure 2.

In addition, TDP-43 exists not only in neurons, but also in peripheral glial cells. They activate the NF-kB pathway, leading to cellular inflammatory responses and neuronal damage [120, 121].

6.5 Chronic stress disrupts cellular defense mechanisms to oxidative stress

Oxidative stress plays a crucial role in neurodegenerative diseases, including Alzheimer's disease (AD), Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS), and Huntington's Disease (HD)[122]. The redox balance of the body is destroyed with increasing age, genetic, and environmental risk factors. Stress caused by various external environmental factors can lead to an increase in ROS in the

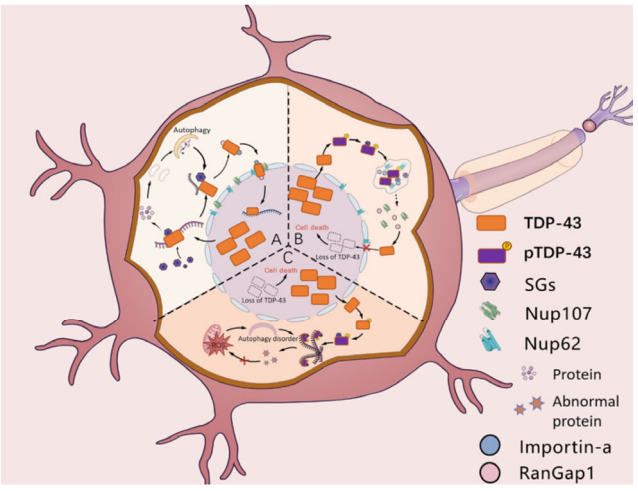


Figure 2 TDP-43 nuclear-cytoplasmic translocation in neurons under three different stress conditions

A. TDP-43, under normal stress, translocates from the nucleus to cytoplasm and signals pathways to combat the stress response. After cessation of stress, cells clear SGs through autophagy, and TDP-43 translocates to the nucleus by homing on Nup107/Nup62 (the nucleopore component) assisted by the transporter Importin-a/RanGap1. B. Under chronic stress, TDP-43 is phosphorylated into pTDP-43 in the cytoplasm, and Nup62/Importin-a soldiers and SGs are recruited to form pTDP-43 /SGs droplets. This causes mislocalization of Nup107 and RanGap1 in the cytoplasm and ultimately prevents TDP-43 from returning to the nucleus. Loss of TDP-43 leads to cell death. C. Long-term/chronic oxidative stress can lead to mitochondrial autophagy dysfunction, causing the accumulation of pTDP-43/SGs aggregates that cannot be cleared properly. Abnormal accumulation of pTDP-43/SGs in the cytoplasm leads to many abnormally functioning gene products (most of which are mitochondrial proteins encoded by the nuclear genome), which cause mitochondrial dysfunction and oxidative mitochondrial damage. Thus, causing autophagy dysfunction and the failure to clear pTDP-43/SGs aggregates.

body [123–125]. Neurons are more susceptible to oxidative stress than other cells in the body [116]. Studies have found increased oxidative stress in the brains of ALS patients [126], similar to that in cultured neurons [127]. An experiment based on mouse cells treated with H_2O_2 demonstrated the transfer of TDP-43 from the nucleus to the cytoplasm under oxidative stress. Moreover, cytoplasmic aggregation of TDP-43 may be related to mitochondrial dysfunction [116].

Mitochondria utilize oxygen to generate energy, and this process is the primary source of endogenous ROS. During periods of stress, cellular metabolism intensifies, leading to the

excessive production of endogenous ROS [128]. ROS refers to a group of free radicals that are centered on oxygen molecules. Low levels of ROS play a crucial role in the physiological processes of cells. However, excessive ROS production can result in oxidative stress, leading to cellular damage [129]. Cells possess a range of defense mechanisms to counteract oxidative stress damage. Among these, the phase II antioxidant response is considered the most significant cellular pathway. This response is regulated by the transcription factor Nrf2, which plays a crucial role in cellular antioxidant defense [130]. Nrf2, a transcription factor, crucially regulates numerous enzymes and proteins involved in the body's REDOX reactions. It achieves this by modulating the composition and induction of the EpRE regulatory genes. The Nrf2-EpRE pathway is of significant importance in maintaining cellular oxidative balance [131]. Under stress, motor neurons release fibroblast factor 1 (FGF-1), which activates astrocytes and promotes the expression of nerve growth factor. This, in turn, modulates Nrf2 expression and function. However, during chronic stress, long-term oxidative stress and the long-term activation of FGF-1 in astrocytes lead to Nrf2-EpRE pathway dysfunction; the interaction between normal neurons and glial cells is destroyed, causing neuronal degeneration [132].

Oxidative stress induces cytoplasmic aggregation of TDP-43, a consequence of which is mitochondrial dysfunction and ROS elevation (increased oxidative stress). Such stress further enhances the accumulation of TDP-43, thus forming a vicious feedforward cycle and driving the occurrence and development of MND [116].

6.6 Mitochondrial dysfunction causes neural death via disruption of calcium homeostasis

Abnormalities in oxidative phosphorylation, calcium buffering, and mitochondrial transport within the CNS have been identified in previous studies on individuals with MND, suggesting that mitochondrial dysfunction may play a significant role in the development of MND [133]. Mitochondrial function is important in the CNS, and although the brain represents only 2% of the body's weight, it consumes 20% of the body's ATP. In neurons, the mitochondrial buffer Ca^{2+} plays an important role in Ca^{2+} homeostasis, phospholipid biogenesis, and apoptosis regulation [133]. It is worth noting that the physiological functions of mitochondria are interrelated in normal and diseased conditions. Oxidative stress in the CNS leads to reduced mitochondrial ATP output and dysfunction of Ca^{2+}-ion channels in the mitochondrial membrane, leading to Ca^{2+} overload. High Ca^{2+} levels cause neuronal cell death through the formation of osmotic transition pores and disrupted transmembrane potentials [134]. Excess Ca^{2+} also degrades organelle structures and proteins by activating conjugated proteinases and accelerating neuronal cell death [135].

6.7 Stress-mediated gut dysbiosis associated with MND

The gut and brain are highly interconnected, and there is a strong association between disruption of the gut microbiota and various neurodegenerative diseases. The vagus nerve, the longest nerve in the human body, crucially connects the digestive system and the CNS [136]. Indeed, both preclinical and clinical data have established a connection between gut dysbiosis and various neurodegenerative diseases, including MND [137].

Stress affects the composition of the gut microbiome [138]. SOD1G93A mice, a typical experimental model of MND, spontaneously exhibit motor symptoms by about 4 months of age and reach the terminal stage of the disease by about 6 months of age. Using this model, Wu

et al. observed that before the onset of MND symptoms, intestinal intercellular connections were disrupted, the expression of adhesion and compact junction proteins was significantly reduced, and intestinal permeability was increased (manifesting as clinical intestinal fistula). The abundance of butyrate Butyrivibrio Fibrisolvens, Escherichia coli, and Firmicutes was reduced in the guts of these mice. Subsequent experiments demonstrated that feeding sodium butyrate to SOD1G93A mice enhanced intestinal epithelial function, improved intestinal integrity, and extended their lifespans [139, 140]. In addition, MND progressed faster in SOD1G93A mice treated with broad-spectrum antibiotics or in sterile SOD1G93A mice [141]. Germ-free mice are more stress-responsive [142]. Furthermore, serum niacinamide (NAM) levels were significantly reduced in MND patients. Colonizing mice with Akkermansia muciniphila(AM) bacteria increased NAM levels, mitigating the progression of MND; however, their survival was not significantly affected [141]. Thus, microbial-derived metabolites, including butyrate and niacinamide, may improve disease progression in MND patients.

The above animal experiments provide evidence confirming that MND and gut microbiome health are associated. Further experiments are required to establish whether gut dysbiosis induced by stress affects the progression of MND.

6.8 Stress destroys BBB integrity leading to neurodegeneration

The BBB and the blood-spinal cord barrier stabilize the CNS microenvironment. These barriers form the basis of all neurophysiological processes and guarantee immunity in the CNS [143]. In the pathogenesis of MND and other neurodegenerative diseases, the permeability of these barriers is affected by the abnormal activation of microglia, inflammatory responses, oxidative stress, intestinal microbial disorders, and physical injury, leading to the occurrence and development of diseases [144].

Almost all neurological diseases are closely related to the BBB. Destruction of the BBB may predate neurological disease [145–147]. Various forms of stress play important roles in triggering the destruction of BBB [148–151].

Different forms of stress, such as acute, chronic, and drug-induced, downregulate connexins on the BBB, which leads to a leaky BBB. This subsequently promotes brain inflammation, neurodegeneration, cognitive, emotional, and behavioral disorders [149]. In some cases of MND, destruction of the BBB and consequent leakage of blood-derived proteins into the CNS occur [152]. For instance, leaked hemoglobin intensifies oxidative stress in the CNS and causes neurotoxicity [153].

7 Stress management in patients with MND benefits prognosis

Sometimes exercising or being physically active can effectively alleviate stress. Appropriate physical exercise can have antianxiety and antidepressant effects, thereby reducing stress levels and helping to maintain a positive mood [152]. Patients who suffer from sleep deprivation or poor-quality sleep often experience heightened stress levels. Therefore, psychological interventions and the judicious use of psychotropic drugs are sometimes necessary [153]. Furthermore, adopting a healthy diet and lifestyle can contribute to stress reduction in patients. For instance, a well-balanced diet and probiotic therapy can help maintain the equilibrium of the gut microbiota, thereby reducing the impact of the gut-brain axis on the CNS [135]. Hence, healthcare professionals should emphasize stress management strategies for patients, as this approach may help slow down the progression of MND and improve the quality of life for MND patients.

Oxidative stress plays a crucial role in the pathogenesis of MND. Although the use of antioxidants in MND treatment is a relatively new approach, edaravone has been clinically used as an antioxidant. However, conclusive results regarding the effectiveness of edaravone have not yet been achieved [154].

8 Conclusions

Numerous studies have consistently established a strong association between psychological and physiological stress and the incidence, progression, and prognosis of MND. The detrimental effects of chronic or severe stress on motor neurons are well documented, encompassing mechanisms such as HPA axis dysregulation, microglial activation, disruption of the BBB, mitochondrial dysfunction, excessive production of ROS, tau protein accumulation, and gut dysbiosis. These mechanisms collectively contribute to the worsening of MND and ultimately lead to unfavorable outcomes. Therefore, in clinical practice, it is crucial for physicians to thoroughly evaluate patients' medical histories to ascertain the presence of various stressors. When addressing adverse stress reactions in MND patients, healthcare professionals should prioritize stress management in addition to relying on conventional treatment methods. Effective communication, the provision of practical recommendations, and the judicious use of psychotropic drugs (in accordance with established protocols) can help alleviate the psychological and physiological burdens experienced by patients, thereby minimizing or eliminating stress.

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Author contribution

Chenyang Lu analyzed the data and prepared the first draft of the manuscript. Chenyang Lu and Xingshun Xu participated in the conception and design of the study, Xingshun Xu constructively revised the manuscript; Chenyang Lu participated in data collection and organization; Xingshun Xu participated in and supervised the study throughout, and they share corresponding authorship. All authors commented on previous versions of the manuscript and approved the final version.

Declaration of conflicting interests

The authors declare no conflict of interest.

Data availability statement

There is no data for this review.

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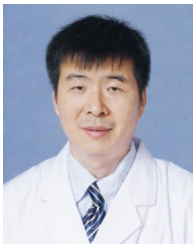
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