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Review

Cerebellum in neurodegenerative diseases: Advances, challenges, and prospects

Guangdong Liu,[1] Cui Yang,[1] Xin Wang,[1] Xi Chen,[1] Huaibin Cai,[2] and Weidong Le[1,3,*]

SUMMARY

Neurodegenerative diseases (NDs) are a group of neurological disorders characterized by the progressive dysfunction of neurons and glial cells, leading to their structural and functional degradation in the central and/or peripheral nervous system. Historically, research on NDs has primarily focused on the brain, brain stem, or spinal cord associated with disease-related symptoms, often overlooking the role of the cerebellum. However, an increasing body of clinical and biological evidence suggests a significant connection between the cerebellum and NDs. In several NDs, cerebellar pathology and biochemical changes may start in the early disease stages. This article provides a comprehensive update on the involvement of the cerebellum in the clinical features and pathogenesis of multiple NDs, suggesting that the cerebellum is involved in the onset and progression of NDs through various mechanisms, including specific neurodegeneration, neuroinflammation, abnormal mitochondrial function, and altered metabolism. Additionally, this review highlights the significant therapeutic potential of cerebellum-related treatments for NDs.

INTRODUCTION

Neurodegenerative diseases (NDs) are characterized by the progressive dysfunction of neuronal structure and function in the nervous system, with the highest incidence among the elderly. Patients with NDs exhibit high mortality and morbidity rates, and they are currently incurable.[1]

The cerebellum, situated beneath the cerebral hemispheres, consists of two hemispheres and a central vermis. At the cellular level, the cerebellum is rich in granule cells (GCs), Purkinje cells (PCs), and various types of glial cells. Traditionally, the cerebellum has been considered a structure controlling movement, such as motion, gait, posture, and balance. However, increasing research in recent years has highlighted the cerebellum's significant non-motor functions, including cognitive, behavioral, and emotional processing.[2] Cerebellar lobules VI, VII, Crus I, and Crus II have been shown to be associated with cognition and emotion.[3,4] The cerebellum and cerebrum are connected via the cerebello-thalamo-cortical (CTC) circuit, with the functional connectivity (FC) networks of the cerebral cortex mapped to distinct cerebellar regions.[5] In NDs, the misfolding and abnormal aggregation of pathogenic proteins, along with their formation and propagation, inevitably impact the cerebellum as well.[6]

In this review, we summarize the relationship between various NDs and the cerebellum, including Alzheimer's disease (AD), Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS), Niemann-Pick C (NPC) disease, Huntington's disease (HD), and frontotemporal dementia (FTD), with a focus on the pathological and biochemical changes in the cerebellum associated with these diseases. The cerebellum is implicated in ND (Table 1), so treatments targeting the cerebellum would be valuable in treating these diseases.

CEREBELLUM AND NDs

AD and cerebellum

AD is predominantly recognized for its debilitating impact on memory and cognitive functions.[38] While past research has mainly focused on the cerebrum and the hippocampus, emerging studies reveal the cerebellum's role in AD. The changes in cerebellar gray matter volume in AD patients are related to disease progression.[7] Our team's previous research reveals electrophysiological alterations in the cerebellum of AD-related APP/PS1 mice before any pathological changes.[39] In the early stages of AD, the cerebellum may have already been affected by amyloid β-protein (Aβ) toxicity, subsequently impacting motor functions.[40] Changes in cerebellar structure and function may be related to disease progression and could aid in the early diagnosis of AD.

[1]Institute of Neurology, Sichuan Academy of Medical Sciences-Sichuan Provincial People's Hospital, School of Medicine, University of Electronic Science and Technology of China, Chengdu 610054, China
[2]Transgenic Section, Laboratory of Neurogenetics, National Institute on Aging, National Institutes of Health, Bethesda, MD 20892, USA
[3]Shanghai University of Medicine & Health Sciences Affiliated Zhoupu Hospital, Shanghai 200237, China
*Correspondence: wdle@sibs.ac.cn
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Table 1. Clinical evidence linking cerebellum to neurodegenerative diseases

Disease	Changes and functions of cerebellum	Reference
Alzheimer's disease	Cerebellar atrophy	Toniolo et al.[7]; Chen et al.[8]
	Impairment of cortico-cerebellar functional connections	Tang et al.[9]
	Aβ and phosphorylated Tau deposits	Sepulveda-Falla et al.[10]
	Purkinje cell loss	Sepulveda-Falla et al.[11]
	Activation of microglia and astrocytes	Singh-Bains et al.[12]
Parkinson's disease	Cerebellar atrophy	Ma et al.[13]; Kerestes et al.[14]
	Early cerebellar functional connectivity changes, associated with cognitive impairment	Dan et al.[15]
	Associated with rest tremor and gait disorders	Piccinin et al.[16]; Maiti et al.[17]
	α-synuclein	Seidel et al.[18]
	Purkinje cell injury	Hartstone et al.[19]
	Dopaminergic transmission markers' expression levels decrease	Hurley et al.[20]
Amyotrophic Lateral Sclerosis	Cerebellar atrophy	Gellersen et al.[21]
	Associated with motor and cognitive impairment	Consonni et al.[22]
	Insoluble and ubiquitinated p62 positive aggregates	Al-Sarraj et al.[23]
	FUS RNA-binding protein expression	Tateishi et al.[24]
	Purkinje cell loss	Tan et al.[25]
	Activation of microglia and astrocytes	Sala et al.[26]
Niemann-Pick C disease	Cerebellar atrophy	Bowman et al.[27]
	Lysosome damage	Chung et al.[28]
	Purkinje cell loss	Sarna et al.[29]
Huntington's disease	Cerebellar atrophy	Ruocco et al.[30]
	The progression of HD is positively correlated with the degree of cerebellar atrophy.	Ruocco et al.[31]
	Associated with motor dysfunction and psychiatric symptoms	Rees et al.[32]
	Purkinje cell loss	Singh-Bains et al.[33]
	A significant loss of the presynaptic marker synaptic vesicle protein 2A	Delva et al.[34]
Frontotemporal Dementia	Cerebellar atrophy	Guo et al.[5]
	The highest DPR load	Quaegebeur et al.[35]
	Associated with behavioral and cognitive disorders.	Chen et al.[36]
	Associated with disease progression	van Blitterswijk et al.[37]

Clinical symptoms and cerebellum

Cognitive and psychiatric disorders in AD patients are linked to the cerebellum.[41] Cerebellar degeneration correlates with memory impairments in patients with mild cognitive impairment (MCI).[42] The cerebellum has a higher predictive value for MCI than changes in the cerebral cortex.[43,44] Significant morphological changes in PCs of the anterior lobe in AD patients may affect cognitive functions.[45] Recent research has found that genes related to intelligence and cognitive functions are expressed in the cerebellum.[46,47] The cerebellum may regulate cognitive functions in the early stages of AD.[48]

AD patients carrying the APOE4 variant exhibit a local reduction in cerebellar volume and thinner cortex.[49] The cerebellum may influence motor dysfunction symptoms of AD. Most patients with the PS1 E280A variant present symptoms of cerebellar ataxia.[10] AD-related TgCRND8 mice exhibit significant deficits in motor coordination and balance.[50] Five-month-old APP/PS1 mice begin to show rotarod and balance beam performance impairments.[51] Twelve-month-old APP/PS1 mice display evident motor dysfunctions.[52] PS1-FAD mice exhibit mild ataxia before Aβ deposition in the cerebellum.[11]

In asymptomatic preclinical AD and MCI patients, increased cerebellar FC may represent functional compensation.[53] Increased cerebellar activation in MCI patients may compensate for defects in the brain-cerebellar circuit.[54] The cerebellum's reserve and compensatory mechanisms could have neuroprotective value.[55] As the disease progresses to later stages, cortico-cerebellar FC is significantly disrupted in AD patients, accompanied by a marked decline in cognitive function.[9,56] The disruption of cerebellar FC may be associated with pathological

changes in AD. Cerebrospinal fluid phosphorylated Tau (p-Tau) and Aβ42 disrupt synapses and cortical networks, leading to cognitive impairment.[57] Additionally, Aβ influences brain-cerebellar FC.[58] In AD, the cerebellum is associated with cognitive and motor disorders, and significant changes may occur early in the cerebellum. The cerebellum's compensatory mechanisms could help alleviate clinical symptoms in the early stages.

Aβ and Tau changes in AD cerebellum

AD patients have Aβ and p-Tau deposits in the cerebellum.[10,11] Aβ plaques begin to appear in the cerebellum ten years before the onset of autosomal dominant AD.[59] The cerebellar Aβ42 correlates with disease progression in AD patients.[60] In APP/PS1 mice, soluble Aβ42 levels at two months of age are about half that of the cerebral cortex, and at eight months, soluble Aβ42 levels are 40% higher than in the cerebral cortex.[61] Numerous studies demonstrated that APP expression level in the cerebellum of AD mice is 1.1 times that of the cerebral cortex and 1.6 times that of the hippocampus, with molecular layer Aβ plaques appearing and increasing with age.[52,62] In patients with AD, fragmentation of the Golgi apparatus in cerebellar PCs is associated with abnormal protein aggregation and synaptic dysfunction.[63] Typical AD pathological changes can be found in the cerebellum of patients and animal models, correlating with the disease progression.

Neurodegeneration in AD cerebellum

The cerebellum contains various cell types and exhibits distinct atrophy in AD patients.[8] The correlation between Aβ42 deposition and PC damage has been observed in AD patients.[60] AD patients have shown a loss of PCs and a significant decrease in dendritic branching density.[11,64] Additionally, AD patients exhibit defects in cerebellar calcium-binding proteins and neurotrophic receptors.[65] However, one study showed that the total volume of the cerebellum decreased by 12.7% in AD without changes in the number of PCs.[66] The cause of this phenomenon may be related to patients at different stages of the disease. The proliferation of astrocytes and activation of microglia have been observed in the cerebellum of AD patients.[12] The PC loss in APP/PS1 mice cerebellum occurred as early as five months of age.[51] In the AD cerebellum, loss of PCs and GCs, activation of microglia, and proliferation of astrocytes often occur.

Mitochondrial and oxidative stress in AD cerebellum

Redox imbalance is shown in the cerebellum during the preclinical and MCI stages of AD patients.[67] Mitochondrial function in the cerebellum of AD patients is abnormal.[11] Concurrently, an abnormal accumulation of reactive oxygen species (ROS) in the cerebellum of AD patients impairs cognitive function.[67] Our previous research has revealed that mitochondrial dysfunction and oxidative stress can mutually exacerbate each other in the brains of AD, a process that may also occur in the cerebellum.[68] Mitochondrial abnormalities appear in the cerebellum of 18-month-old APP/PS1 mice.[52] Genes related to mitochondrial dysfunction significantly change in the cerebellum of 7-week-old 5xFAD mice.[69] Additionally, NADPH oxidase and oxidative stress are activated in the cerebellum of TgCRND8 mice.[50] The early AD cerebellum exhibits mitochondrial dysfunction and increased oxidative stress.

Metabolic disturbance and neurotransmitter changes

Brain metabolic dysregulation is related to AD. Metabolic increase in the cerebellum is observed during the transition from MCI to AD.[70] High metabolism is found in AD cerebellar regions.[71] In the cerebellum of APP/PS1 mice, extensive metabolic changes have been observed, mainly the dysregulation of energy and amino acid metabolism.[72] Furthermore, in the 3xTg-AD mice cerebellum, proteins related to energy metabolism are altered.[73] In AD mice, there is dysregulation of cholesterol metabolism in the cerebellum, characterized by elevated levels of the cholesterol precursor desmosterol and cholesterol metabolites, which may be associated with the Seladin-1/Dhcr24 gene.[74] Dysregulation of noradrenergic modulation in the cerebellum of 2-month-old TgCRND8 mice suggests early neurotransmitter changes.[50] Cholinergic dysfunction is one of the hallmark features of AD. The cerebellum may directly impact the cholinergic function of AD patients.[75] In APP/PS1 mice, abnormal expression of Ly6/uPAR proteins in the cerebellum leads to dysfunction of the cholinergic system.[76] In AD, the cerebellum exhibits various metabolic dysregulations and neurotransmitter imbalances.

AD cerebellum displays a number of pathological and biochemical changes (Figure 1). In the early stages, the cerebellum may play a compensatory role, slowing the progression of clinical symptoms.[54,55] The AD cerebellum exhibits typical Aβ and Tau pathology, relating to cognitive and behavioral changes. Changes in mitochondria, oxidative stress, and metabolism in the AD cerebellum are significant and may occur early in the disease.[11,67,70] Furthermore, loss of PCs, reduction in GCs, activation of microglia, and proliferation of astrocytes are observed in the AD cerebellum. The expression levels of APP in the cerebellum and the cerebrum are comparable during the same period, but Aβ plaques are sparser in the cerebellum.[77] Cerebellum's unique cell types and cytokines may provide the intrinsic mechanisms of delayed AD pathological changes. It seems that structural and functional changes occur in the AD cerebellum, and its FC with other brain regions also changes.

PD and cerebellum

PD Patients exhibit clinical symptoms, including bradykinesia, rigidity, tremors, gait disturbances, cognitive impairments, and psychiatric symptoms. Pathophysiological changes in PD involve abnormalities in multiple brain regions. The cerebellum contains dopamine receptors and receives dopaminergic projections, with the pathway between the cerebellum and the ventral tegmental area of the midbrain transmitting dopamine to the prefrontal cortex.[78] There are anatomical connections between the cerebellum and the basal ganglia.[79] In PD,

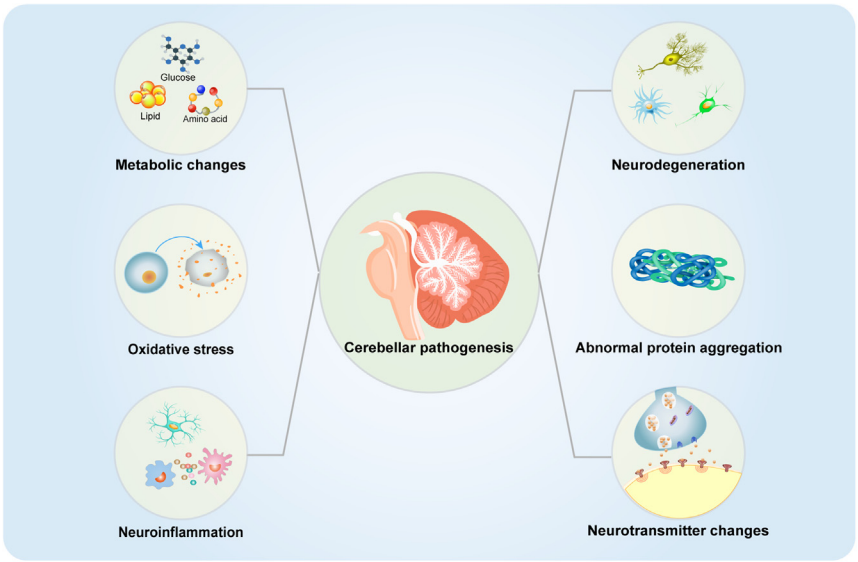

Figure 1. Major pathological and biochemical changes in the cerebellum in NDs

This figure summarizes the reported cerebellum-related pathological and biochemical changes in NDs. Neurodegeneration, metabolic disorders, neuroinflammation, oxidative stress and abnormal protein aggregation, are related to the occurrence and development of NDs.

α-synuclein and dopaminergic dysfunction are present in the cerebellum.[80] PD patients exhibit notable cerebellar gray matter atrophy, aiding in disease diagnosis.[13] Cerebellar changes in PD patients may relate to clinical symptoms and disease staging, gradually decreasing in volume as the disease progresses.[14] Different cerebellar subregions in PD patient subtypes exhibit varied change patterns, facilitating subtype differentiation.[81] Increased activation of the cerebellum in PD patients may reflect a compensatory mechanism.[82] In the early stages of PD, the basal ganglia-cerebellar connection compensates for deficits in the nigrostriatal-basal ganglia-cortical circuit, but the cerebellar circuit function weakens as the disease progresses to later stages.[83] Overall, cerebellar abnormalities may broadly impact the progression of PD.

Psychiatric symptoms and cerebellum

The cerebellum of PD patients affects cognitive function.[84] PD patients show early cerebellar FC changes, potentially related to cognitive deficits.[15] In patients with PD, cerebellar vermis FC is related to cognitive function.[85] Moreover, cerebellar changes can be used to distinguish PD patients with or without MCI.[86] Increased FC between the caudate and cerebellum helps alleviate cognitive impairments in PD patients.[87] The cerebellum may be involved in depression and anxiety. The cerebellum is crucial to the mechanism of depression in PD.[88] Changes in cerebellar FC are significantly related to anxiety in PD patients.[89] Depression is inversely associated with right cerebellar IX volume, and anxiety is inversely associated with right lobule VIII volume.[13] Cerebellar FC aids in diagnosing PD patients with hallucinations.[90] Collectively, the cerebellum is related to the emergence of psychiatric symptoms in PD, including cognition, anxiety, depression, and hallucinations.

Motor impairment and cerebellum

Cerebellar dysfunction may be associated with motor dysfunctions, including rest tremors and gait instability. In PD patients, the cerebellum is implicated in the mechanism of rest tremors.[16] Moreover, cerebellar lobule IV correlates with the severity of tremors in PD patients.[91] Dopamine-resistant tremors may be related to the cerebellum.[92] Increased FC between the left cerebellar dentate nucleus and other brain areas is observed in PD patients with motor dysfunctions.[93] Increased FC among cerebellar structures in PD may have compensatory effects for restoring motor functions.[94] Cerebellar vermis dysfunction is related to gait disturbances.[17] FC in the cerebellar motor areas correlates with the severity of freezing of gait in PD.[95] Clearly, the cerebellum's involvement is linked to the occurrence and severity of motor dysfunctions in PD.

Neurotransmitter changes in PD cerebellum

The cerebellum contains high levels of dopamine and widely distributed dopamine receptors.[96] Aldose reductase, associated with dopamine synthesis, shows a significantly reduced level in the PD cerebellum.[97] Dopaminergic transmission expression levels are decreased in the PD cerebellum.[20] Early compensatory cholinergic upregulation occurs in the cerebellum of PD patients.[98] Additionally, the cerebellar neurotransmitter systems in PD are related to cognitive functions.[78] The cerebellar noradrenergic system may relate to cognitive, emotional, essential tremor, and motor in PD.[99] Gamma-Aminobutyric Acid (GABA) level in the cerebellum are related to cognitive decline in PD patients.[100] In PD rats, an imbalance between excitatory and inhibitory amino acids in the cerebellum is associated with redox imbalance and a significant increase in TNF-α.[101] Various neurotransmitter disturbances occur in the PD cerebellum, correlating with clinical symptoms.

Neurodegeneration in PD cerebellum

Intracellular aggregation of α-synuclein is a hallmark pathological change in PD. Patients with α-synucleinopathy exhibit cerebellar connectivity disorders.[102] Neurons and oligodendrocytes in the PD cerebellum are affected by α-synuclein.[18] A significant loss of PCs is observed in essential tremor.[19] Changes in the cerebellar climbing fiber-PC synaptic connections correlate positively with the severity of essential tremor.[103] GABA neurons and oligodendrocytes in the PD mouse cerebellum are enriched with PD-related genes.[104] It looks like various cells in the PD cerebellum undergo morphological and functional changes.

Metabolic changes and PD cerebellum

The cerebellum exhibits hypermetabolism in PD monkey models.[105] Similarly, PD patients with dysphagia also show increased cerebellar metabolism.[106] Cerebellar metabolism increases before the first fall in PD patients.[107] Disease progression in PD patients is associated with increased metabolism of the cerebellum.[108] PD patients exhibit changes in oxygen metabolism in the cerebellum.[109] During the cognitive impairment stage of PD, regional cerebral glucose metabolism in the cerebellum increases.[110] Cerebellar inosine increases, while tyrosine and pantothenate decrease in PD dementia patients.[111] Metabolic changes in the cerebellum contribute to the early diagnosis and disease course evaluation of PD.

The cerebellum in PD undergoes significant atrophic changes. The compensatory function of the cerebellum can delay clinical symptoms in the early stages, but this compensatory ability may be lost in the later stages. Cerebellar abnormalities are related to motor and psychiatric symptoms. The PD cerebellum is also affected by α-synuclein. Neurotransmitter changes and metabolic alterations occur in the PD cerebellum, correlating with disease progression. In summary, studies on PD patients and animal models indicate that the cerebellum is affected in PD and has a broad impact on disease progression (Figure 1). Exploring cerebellar changes in PD can deepen our understanding of the disease and aid in its treatment and symptom improvement.

ALS and cerebellum

The characteristic pathological changes in ALS include glutamate excitotoxicity, protein misfolding and abnormal aggregation, inflammation, apoptosis, mitochondrial dysfunction, and oxidative stress.[112] Over the past decades, pathogenic mutations in several genes, including C9orf72 on chromosome 9, superoxide dismutase 1 (SOD1), TAR DNA-binding protein (TDP-43), FUS RNA-binding protein (FUS), and several others, have been identified in ALS.[113] Autopsy results of patients with FUS mutations show FUS expression and neurodegenerative changes in the cerebellum.[24] SOD1 mutations are the second most common mutation in ALS, with some patients exhibiting cerebellar ataxia symptoms.[114] GFP-PR28 transgenic mice partially mimic the pathological features of ALS, showing a reduction in PCs and cerebellar inflammation.[115]

Cerebellar atrophy and compensation

The cerebellar volume reduction and significant atrophy are observed in ALS patients.[21] A GWAS meta-analysis also identifies the cerebellum as a functionally implicated organ in ALS.[116] Symptoms in ALS patients may be related to changes in different cerebellar subregions. The involvement of various cerebellar areas may be associated with motor or cognitive impairments in ALS.[22] The motor symptoms in ALS patients are related to atrophy in the lower lobules.[117] The anterior lobules I-V of the cerebellum are implicated in sporadic ALS patients, while the posterior lobe and vermis are affected in carriers of the C9orf72 mutation.[118] The cerebellum may play compensatory roles in ALS patients. The cerebellum in ALS patients may mitigate clinical symptoms in the early stages, but this compensation may be depleted as the disease progresses.[119] The cerebellum is affected in ALS and the alterations of the cerebellum correlate with the changes of clinical symptoms.

Protein aggregates in ALS cerebellum

The repeated amplification of hexanucleotide in C9orf72 transforms into dipeptide repeat proteins (DPRs), forming insoluble and ubiquitinated p62 positive aggregates that are highly expressed in the cerebellum of ALS patients.[23] The cerebellum of C9-ALS may initially be affected by DPRs.[120] The ALS cerebellum expresses p62 positive and ubiquitinated aggregates, but there are no TDP-43 positive inclusions.[121] RAN translation produces five types of repeat dipeptide proteins (GP, GA, GR, PR, PA), constituting the main components of TDP-43-negative and p62-positive inclusions.[122] And inclusions of GP and GA are abundant in the cerebellum.[123]

Neurodegeneration in ALS cerebellum

Significant loss of PCs in the vermis of ALS patients, along with ATXN2 repeat expansions, has been observed.[25] Overexpression of SOD1 leads to PC degeneration.[124] GFP-PR28 transgenic mice, MATR3 S85C knock-in mice, and Tbk1-NKO mice partially mimic ALS neuropathological features, with significant reductions and morphological abnormalities in PCs.[115,121] ALS patients exhibit increased reactive astrocytes and activated microglia.[26] Moreover, microglia activation in the cerebellum of SOD1 mutation patients has been reported.[125] Loss of PCs, along with increased microglia and astrocytes, occurs in the ALS cerebellum.

Neuroinflammation and oxidative stress in ALS cerebellum

Activation of microglia and neuroinflammation have been detected in the cerebellum of SOD1 mutation patients.[125] In ALS Wobbler mice, abnormal protein aggregation in the cerebellum leads to elevated expression of IL-1β and TNF-α, an increase in microglial and astrocytic

cells, ultimately resulting in motor deficits.[126] Moreover, inflammatory changes are also found in the cerebellum of GFP-PR28 mice.[115] ALS patients exhibit oxidative stress significant inflammation and increased oxidative stress in the cerebellum.[127]

The ALS cerebellum is affected by the typical pathology of ALS, exhibiting structural and functional abnormalities (Figure 1). Changes in the ALS cerebellum relate to clinical symptoms, and the cerebellum may have compensatory functions, which could be depleted in the later stages. Inflammation is evident in the ALS cerebellum. The contribution of the cerebellum to ALS requires careful consideration, and further study of this largely overlooked neuroanatomical area is warranted.

NPC disease and cerebellum

The cerebellum is severely affected in the early stages of NPC disease.[128] Loss of cerebellar volume is related to the severity of clinical symptoms in NPC patients.[27] In Npc1 mice, increased oxidative stress in the cerebellum causes lysosomal membrane damage and alterations in permeability, leading to leakage of lysosomal contents and ultimately resulting in cerebellar degeneration.[28] In Npc1 mice, defects in Sonic hedgehog signaling in the cerebellum lead to proliferative deficits in GCs and abnormalities in cerebellar morphology.[129]

Neurodegeneration in NPC cerebellum

PC deaths occur in the cerebellum of NPC patients, increasing in number as the disease progresses.[29] PCs are particularly sensitive to NPC1 deficiency and undergo degeneration early in the disease, while early activation of microglia may precede PC degeneration.[130] In the cerebellum of Npc1 mice, the activation and interactions of microglial cells promote the degeneration of PCs.[131] The death of cerebellar PCs is associated with increased levels of caspase 1, caspase 3, NPC2, LipA, apoE, apoD, GFAP, and TNF-α.[132] Microglial activation precedes neuronal dysfunction in presymptomatic 3-week-old Npc1 mice.[133] There is a significant early increase in astrocytes in the cerebellum of Npc1 mice.[134] Additionally, proliferative defects in cerebellar GCs and impaired differentiation of cerebellar glomeruli are reported in Npc1 mice.[129] In the cerebellum of Npc1 mice, elevated levels of cathepsins, cytochrome *c*, and Bax2 play a role in neuronal degeneration.[135]

Lipid metabolism disorders and NPC cerebellum

NPC1 disease is characterized by neuronal lipid storage in the cerebellum. Elevated levels of the gangliosides GM2 and GM3 in the cerebellar posterior lobules of NPC1 disease are associated with lipid alterations and cell death.[136] In Npc1 mice, a significant increase in GM2 in deep cerebellar nuclei (DCN) neurons and the absence of the lipid raft marker Flot2 expression lead to cellular dysfunction.[137] In the cerebellum of Npc1 mice, cholesterol imbalance affects the endocannabinoid (eCB) system, and defects in eCB signaling can promote disease progression.[138] Obviously, significant lipid metabolism disorders occur in the cerebellum in NPC disease.

Inflammation and oxidative stress in NPC cerebellum

Microglia and astrocytes are activated in the cerebellum in NPC disease. Abnormal interferon expression is detected in the cerebellum of presymptomatic Npc1 mice.[139] Presymptomatic Npc2 mice cerebellum also exhibited neuroinflammation.[140] Presymptomatic Npc1 mice showed abnormal oxidative stress in the cerebellum.[139] In Npc1 mice, oxidative stress in the cerebellum is a major stimulus activating apoptosis.[141] ROS in the cerebellum of Npc1 mice damage the lysosomal membrane, ultimately leading to apoptosis.[28] Oxidative stress and inflammation in the cerebellum of NPC disease can aggravate disease progression.

The primary symptom of NPC disease is progressive cerebellar ataxia. Loss of PCs and GCs and early activation of microglia occur in the NPC cerebellum. NPC cerebellum exhibits lipid metabolism disorders, oxidative stress, and neuroinflammation (Figure 1).

HD and cerebellum

Mutant huntingtin protein is significantly overexpressed in the HD cerebellum.[142] A study suggests that the pathological process of HD may be characterized by multifocal onset, with cerebellar damage potentially being an early event.[143] Both gray and white matter volumes are reduced in the cerebellum of HD patients, showing significant atrophy.[30] Cerebellar involvement is an early event in HD.[144] Furthermore, the progression of HD is positively correlated with the degree of cerebellar atrophy.[31] HD patients exhibit widespread motor and cognitive impairments. Cerebellar changes are associated with motor dysfunction and psychiatric symptoms.[32] Moreover, the posterior superior lobe of the cerebellum in HD is related to emotional symptoms.[145] HD patients exhibit cerebellar atrophy, and cerebellar changes correlate with clinical symptoms.

Cellular and synaptic changes in HD cerebellum

In the HD cerebellum, continuous loss of PCs and neurons is observed.[146] A significant loss of PCs in HD patients with motor symptoms is noted, whereas this change is not observed in patients primarily exhibiting emotional changes.[33] Cerebellar PC dysfunction and death in HD mice are associated with ataxia symptoms.[147] Furthermore, expression of cyclin D1 in the granular layer of HD mice cerebellum is increased, along with upregulation of cell cycle regulatory factors Cbx2, Cbx4, and Cbx8.[148] A significant loss of the presynaptic marker synaptic vesicle protein 2A is observed in HD patients' cerebellum.[34] There are significant cellular and synaptic alterations in the HD cerebellum.

Metabolic changes in HD cerebellum

Hypermetabolism in the cerebellum of HD patients may compensate for motor disorders.[149] In the cerebellum of HD mice, about 11% of metabolites show significant changes.[150] Significant differences in metabolites, mainly affecting amino acid metabolism, are observed in the cerebellum of the HD transgenic sheep model (OVT73).[151] Dysregulation of the urea cycle in the cerebellum of the HD OVT73 sheep model and HD patients results in elevated urea and ammonia levels, causing neurological damage.[152] The demand for fatty acids is reduced in the cerebellum of HD model mice.[153] The cerebellum of HD mice exhibits changes in substance metabolism, including amino acids, fatty acids, and urea.

Cerebellar atrophy in HD occurs early in the disease and is related to disease progression and clinical symptoms. Multiple pathological and biochemical changes are also present in the cerebellum of HD (Figure 1). Extensive metabolic and cellular changes are also evident in the HD cerebellum. It seems that the HD cerebellum undergoes multifaceted changes.

FTD and cerebellum

FTD exists in familial and sporadic forms, with C9orf72 mutation being the most common cause. Loss of C9orf72 expression, formation of DPRs, and RNA foci all contribute to FTD. The cerebellum in C9orf72 shows the highest DPR load.[35] The size of hexanucleotide repeat expansions in the cerebellum of C9orf72-repeat-associated FTD (C9-FTD) correlates with disease duration and severity.[37] Presymptomatic C9-FTD patients also display evident gray matter atrophy in the cerebellum.[154] FTD features focal cerebellar atrophy strongly connected intrinsically to atrophy regions within the cerebral cortex.[5] Different subtypes of FTD involve specific cerebellar lobule alterations rather than global cerebellar atrophy.[155]

In FTD, cerebellar changes are related to behavioral disruptions and cognitive impairments.[36] Cerebellar integrity in C9-FTD patients is associated with attention, language, and executive functions.[156] Abnormalities in cerebello-cortical circuits in C9-FTD play a crucial role in cognitive and behavioral changes.[157] The psychiatric symptoms in C9-FTD patients are associated with cerebellar atrophy.[158] The degree of psychiatric disorders in C9-FTD correlates with cerebellar degeneration.[159] Cortico-cerebellar networks are related to cognitive and psychiatric dysfunctions in behavioral variant FTD (bvFTD).[160] In bvFTD, cerebellar output pathways are related to episodic memory, while input pathways are associated with memory, visuospatial skills, and emotion.[161] Psychiatric symptoms in carriers of C9orf72 and GRN mutations are related to cerebellar atrophy.[162] FTD cerebellum exhibits significant atrophy related to clinical manifestations and disease progression.

CEREBELLUM IS THE TARGET FOR ND TREATMENT

The cerebellum is interconnected with the cortex, frontal lobes, temporal lobes, and parietal cortex regions through multiple closed-loop circuits, participating in the regulation of movement, cognition, and emotion. Transcranial Magnetic Stimulation (TMS) and Transcranial Direct Current Stimulation (tDCS) both contribute to alleviating symptoms of cerebral dysregulation.[163] There are two main hypotheses regarding the effects of TMS on the cerebellum. First, TMS ameliorates abnormal activation in the cerebellar cortex, alters the activity of PCs, and diminishes their inhibitory impact on the CTC pathway. Second, TMS can enhance cerebellar plasticity, increase long-term potentiation effects in the cerebellar cortex, and promote FC between brain regions.[164] Cerebellum-related therapeutic approaches can facilitate the treatment of NDs and improve clinical symptoms (Figure 2).

AD treatment

Cholinergic dysfunction is a hallmark of AD. The cholinergic system in the cerebellum plays a vital role in the normal functioning of the cerebellum.[165] Cerebellar magnetic stimulation may effectively modulate central cholinergic activity in AD patients by activating the CTC pathway.[75] A study showed that 5 Hz repetitive TMS of the cerebellum is a promising treatment method for AD patients.[166] Currently, there is limited research on cerebellum-related treatments for AD patients. Cerebellar therapeutic approaches exhibit significant potential in treating AD, which could help in delaying cognitive and motor dysfunctions in AD patients.

PD treatment

Neurostimulation therapies hold potential value for improving gait dysfunction in patients with PD. Transcranial Electrical Stimulation on the cerebellum can improve gait disturbances in PD patients.[167] Transcranial Alternating Current Stimulation of the cerebellum can reduce resting tremors in PD patients.[168] The tDCS of the cerebellum is a potential intervention for enhancing motor learning in PD.[169] Cerebellar tDCS treatment in PD patients significantly improves gait speed.[170] A single higher-intensity cerebellar tDCS treatment in PD patients can significantly improve balance disorders, but not enhance motor abilities, suggesting that multiple treatments may be necessary to improve motor dysfunction.[171] Five consecutive days of cerebellar tDCS application can improve Levodopa-induced motor disorders in PD patients.[172] In conclusion, the long-term application of cerebellar tDCS therapy can enhance motor function in PD. Furthermore, cerebellar Theta-Burst Stimulation can improve Levodopa-induced Dyskinesias in PD patients, accompanied by a reduction in serum BDNF levels.[173] Cerebellar rTMS treatment has improved tremors in PD patients, with no serious adverse events reported.[164]

Exercise in PD patients can enhance cerebellar activation, thereby improving motor symptoms.[174] Skilled aerobic exercise can increase cerebellar regional cerebral blood flow, thereby improving motor dysfunction.[175] Magnetic and electrical stimulation of the cerebellum in PD can serve as reliable treatment methods to slow disease progression and improve patient symptoms. Physical training can also play a therapeutic role in PD through improvements to the cerebellum.

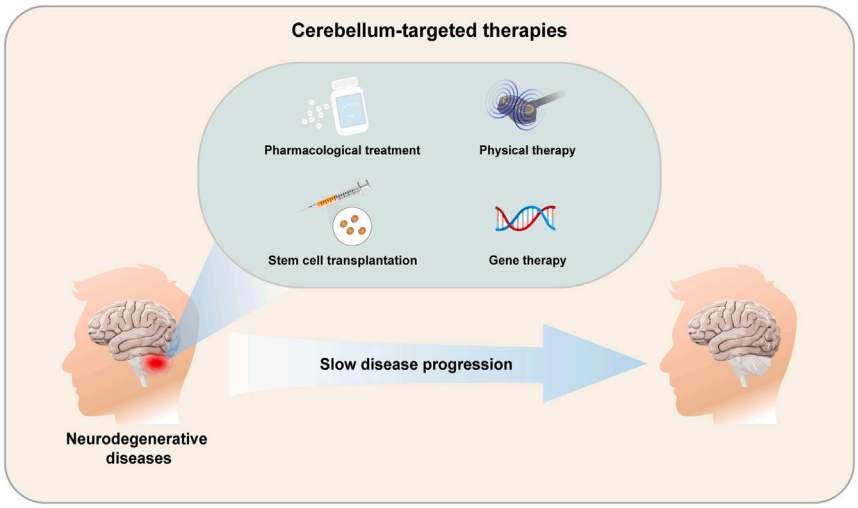

Figure 2. Potential cerebellum-related therapeutic modalities in NDs

Pharmacological treatment, stem cell transplantation, physical therapy, and gene therapy provide effective treatments for cerebellum-related NDs and help improve clinical symptoms.

ALS treatment

Injecting IGF-1 into the DCN of ALS mice reduces ALS neuropathology, and significantly extends the lifespan of ALS mice.[176] Sodium selenite mitigates motor deficits in ALS by inducing mitochondrial autophagy in the cerebellum.[177] Cerebellum-related therapeutic approaches may hold significant potential value for ALS. Cerebellar magnetic and electrical stimulation could be valuable in improving ALS symptoms. However, current studies on cerebellum-related treatments are limited, and future research should be expanded into cerebellar involvement in ALS.

NPC treatment

Cerebellar transplantation of bone marrow-derived mesenchymal stem cells (BM-MSCs) alleviates inflammatory responses in the cerebellum of NPC mice.[178] Injection of BM-MSCs into the cerebellum of ASM-KO mice significantly slows down the loss of PCs.[179] Additionally, BM-MSC transplantation into the cerebellum of NPC mice upregulates neurotransmitter receptors, potentially aiding in synapse formation.[180] Human umbilical cord blood-derived mesenchymal stem cells can inhibit inflammation and apoptotic signaling in the cerebellum, reducing the loss of PCs.[181] Transplantation of adipose tissue-derived stem cells into the cerebellum of NPC mice alleviates inflammatory responses, rescues PCs, and promotes synapse formation, thereby restoring motor coordination.[182]

It is reported Miglustat, the only drug used to treat NPC disease,[183] shows neuroprotective effects on the cerebellum.[27] Intraperitoneal treatment with GSH ethyl ester improves oxidative stress and mitochondrial function in the cerebellum of Npc1 mice, thereby restoring PC activity and alleviating motor dysfunction.[184] The cerebellum is a primary affected area in NPC, warranting further therapeutic approaches targeting on cerebellum.

CONCLUSIONS

NDs pose a significant threat to human health, causing considerable social and economic burdens, and currently remain incurable. In the context of NDs, apart from the primary lesion site, the cerebellum often receives insufficient attention. It is believed that the cerebellum plays a critical role in NDs. First, the cerebellum is affected in NDs and is not an unaffected region. Cerebellar atrophy occurs in these diseases and correlates with disease severity. In some conditions, cerebellar atrophy is evident early on, aiding in early diagnosis. Different subtypes of NDs may exhibit distinct cerebellar changes, facilitating differential diagnosis. The involvement of specific cerebellar regions may lead to particular symptoms. Second, the cerebellum may serve a reserve and compensatory role. It might compensate for clinical symptoms of NDs, slowing disease progression. However, this compensatory ability may be lost in the later stages. Lastly, the cerebellum in NDs undergoes various pathological and biochemical changes, primarily on cerebellar neuron degeneration, neuroinflammation, mitochondrial dysfunction, metabolic disorders, and neurotransmitter changes. These pathological and biochemical changes contribute to the onset and progression of NDs. We have also summarized therapeutic approaches related to the cerebellum in NDs. Cerebellar magnetic and electrical stimulation, physical therapy, stem cell therapy, and pharmacological treatments may contribute to the management of these diseases. In summary, the cerebellum holds significant value for the early diagnosis, treatment, and prevention of disease progression in NDs.

FUTURE DIRECTIONS

In previous research related to NDs, the cerebellum has largely been overlooked. The functional contributions and molecular mechanisms of the cerebellum in NDs remain largely unknown. The neural circuits and functions associated with the cerebellum are still unclear. Further research is needed to understand the pathological changes in the cerebellum during NDs, explore the specific mechanisms of interaction between the cerebellum and other regions of the nervous system, and determine the extent to which cerebellar changes affect clinical presentations. The specificity of cerebellar cells and structures may have unique roles. For example, the cerebellum shows a later appearance of Aβ compared to the cerebral cortex, which may relate to endogenous and exogenous factors. Endogenous factors might include differences in cerebellar cell types, structures, and gene expression, while exogenous factors could involve lymphatic and vascular structures. Further research is required to elucidate the role of cerebellar tissue and structure in the onset and progression of NDs. There is less research on cerebellum-related treatments for AD, ALS, and HD, although several studies have been reported on PD and NPC diseases. Magnetic and electrical stimulation of the cerebellum and stem cell therapy hold great potential for NDs. It is necessary to investigate the value of cerebellum-related therapeutic approaches for NDs further. Cerebellum-related therapeutic approaches may offer a promising and safe option for treating these diseases.

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AUTHOR CONTRIBUTIONS

G.L. conceived the review and drafted the manuscript. C.Y., X.W., X.C., and H.C. helped revise this manuscript; W.L. designed this review concept and helped edit and revise the manuscript. All the authors read and approved the manuscript.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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