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Neonatal Brain Development and Protein Aggregation: Implications for Alpha-Synucleinopathy and Neurodegenerative Diseases

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ABSTRACT

Background: Neonatal brain development is a highly dynamic process characterized by rapid neuronal growth, synaptogenesis, and myelination. Protein homeostasis during this critical period is essential to maintain cellular function and prevent pathological protein aggregation. Alpha-synuclein, a presynaptic neuronal protein, has been implicated in various neurodegenerative disorders, particularly Parkinson's disease and related synucleinopathies.

Methods: This review explores the intersection of neonatal brain development and protein aggregation, focusing on alpha-synucleinopathy and its implications for neurodegenerative diseases.

Results: Recent evidence suggests that early-life protein aggregation may have long-term consequences on neurodegeneration. Dysregulation of proteostasis mechanisms in the neonatal brain may predispose individuals to early alpha-synuclein aggregation, which could act as a priming event for later-life neurodegeneration.

Conclusion: Understanding the developmental origins of alpha-synucleinopathies may aid in identifying early biomarkers and developing neuroprotective strategies to mitigate long-term neurological consequences.

Keywords: *Neonatal brain development, protein aggregation, alpha-synucleinopathy, neurodegeneration, Parkinson's disease.*

1. INTRODUCTION

The neonatal period is a critical window for brain maturation, involving extensive neuronal proliferation, differentiation, and synaptic connectivity. During this stage, the brain undergoes rapid structural and functional development, laying the foundation for cognitive and motor functions later in life. Key processes, including synaptogenesis, myelination, and neuronal circuit formation, are tightly regulated to ensure proper neural network functionality. Disruptions in these processes have been linked to various neurodevelopmental and neurodegenerative disorders [1,2].

One of the fundamental mechanisms maintaining neuronal integrity during neonatal brain development is protein homeostasis, or proteostasis. This is regulated by an intricate network of molecular pathways, including autophagy, the ubiquitin-proteasome system (UPS), and chaperone-mediated protein folding [3]. Autophagy is particularly crucial during neonatal development, as it facilitates the removal of damaged organelles and misfolded proteins, preventing neurotoxicity [4]. Similarly, the UPS ensures the degradation of aberrant proteins, maintaining cellular proteostasis [5]. Dysfunctions in these pathways have been implicated in early-onset neurodegenerative conditions, highlighting their essential role in brain development and disease prevention.

Alpha-synuclein, a presynaptic neuronal protein, plays a key role in synaptic plasticity and neurotransmitter release [6].

Although its physiological function in neonatal brain development remains an area of active research, recent studies suggest that alpha-synuclein is involved in synaptic vesicle trafficking and neuronal differentiation [7]. However, under pathological conditions, alpha-synuclein can misfold and aggregate, forming toxic oligomers and fibrils that contribute to neurodegenerative disorders such as Parkinson's disease, dementia with Lewy bodies, and multiple system atrophy [8,9]. Evidence indicates that disruptions in proteostasis during neonatal brain development may predispose individuals to early alpha-synuclein aggregation, which could act as a priming event for later-life neurodegeneration [10].

Environmental and genetic factors may further influence neonatal protein aggregation and neurodevelopmental trajectories. Perinatal hypoxia, inflammation, and environmental toxins such as pesticides and heavy metals have been shown to exacerbate protein misfolding and aggregation in early brain development [11,12]. Epidemiological studies suggest that prenatal and neonatal exposures to such risk factors increase the likelihood of neurodegenerative diseases in adulthood, reinforcing the need for early detection and intervention strategies [13,14].

This review aims to explore the intricate relationship between neonatal brain development and protein aggregation, focusing on the implications of alpha-synucleinopathy in neurodegenerative diseases. By understanding how early-life disruptions in proteostasis contribute to long-term neurodegeneration, novel therapeutic and preventative strategies may be developed to mitigate the burden of synucleinopathies and related disorders.

2. NEONATAL BRAIN DEVELOPMENT: KEY PROCESSES

2.1 Neurogenesis and Synaptogenesis

Neurogenesis peaks during the perinatal period, with neural stem cells giving rise to neurons that integrate into functional circuits. This process is tightly regulated by intrinsic genetic programs and extrinsic environmental signals [15]. During this period, neural progenitor cells migrate, differentiate, and establish synaptic connections with other neurons to form functional neural circuits [16]. Dysregulation of neurogenesis has been linked to cognitive deficits and neurodevelopmental disorders such as autism and schizophrenia [17].

Synaptogenesis, the formation of synapses between neurons, is another crucial process during early brain development. Synapses are responsible for neuronal communication, and their formation involves complex molecular interactions between pre- and postsynaptic neurons [18]. Activity-dependent synaptic plasticity plays a significant role in refining neural circuits, and excessive or insufficient synapse formation has been implicated in neurological disorders [19]. Synaptic pruning, a process in which weak or redundant synapses are eliminated, further optimises neuronal connectivity and ensures efficient information processing in the brain [20].

2.2 Myelination and Cellular Maturation

Myelination is essential for the proper functioning of the nervous system and involves the ensheathment of axons by oligodendrocytes to facilitate rapid nerve impulse conduction [21]. This process begins prenatally and continues well into adulthood, with the most rapid myelination occurring during infancy [22]. The maturation of oligodendrocytes and myelin sheaths is regulated by signalling pathways such as Wnt, Sonic Hedgehog (Shh), and Notch, which coordinate the differentiation of oligodendrocyte precursor cells into mature, myelinating cells [23].

Disruptions in myelination have been linked to various neurodevelopmental disorders, including cerebral palsy and leukodystrophies, as well as increased susceptibility to neurodegenerative diseases later in life [24]. Studies have shown that perinatal insults such as hypoxia-ischemia, inflammation, and nutritional deficiencies can lead to abnormal myelination patterns, which may predispose individuals to conditions such as multiple sclerosis and Parkinson's disease [25,26]. Recent research suggests that early-life exposure to environmental toxins, including heavy metals and endocrine disruptors, may also impair myelin formation and contribute to long-term neurological deficits [27].

2.3 Protein Homeostasis in Early Brain Development

Protein homeostasis, or proteostasis, is a critical aspect of neonatal brain development, ensuring that proteins are correctly synthesized, folded, and degraded to maintain cellular function. Several interconnected pathways, including the endoplasmic reticulum (ER) stress response, autophagy, and molecular chaperone systems, work in concert to regulate protein turnover and prevent the accumulation of misfolded proteins [28].

The ER stress response is particularly important in neurons due to their high metabolic activity and demand for protein synthesis. Misfolded proteins in the ER trigger the unfolded protein response (UPR), which activates signalling pathways to restore homeostasis or initiate apoptosis if the damage is irreversible [29]. In neonatal brain development, proper regulation of the UPR is essential for neuronal survival and differentiation, and disruptions in this process have been implicated in neurodevelopmental disorders such as Rett syndrome and Fragile X syndrome [30].

Autophagy, a cellular degradation process that eliminates damaged proteins and organelles, also plays a crucial role in maintaining neuronal proteostasis [4]. Autophagy dysfunction has been linked to neurodegenerative diseases such as Alzheimer's and Parkinson's, where impaired clearance of toxic protein aggregates contributes to neuronal death [31].

Studies in neonatal models have demonstrated that autophagy is vital for synaptic pruning and neuronal remodeling, and defects in this pathway may predispose individuals to neurodegenerative conditions later in life [32].

Molecular chaperones, including heat shock proteins, assist in protein folding and prevent aggregation by stabilising nascent polypeptides [33]. During neonatal development, chaperones ensure the proper folding of essential synaptic and structural proteins, promoting neuronal differentiation and circuit formation. A deficiency in molecular chaperones has been associated with increased vulnerability to oxidative stress and protein misfolding disorders [34].

Dysregulation of proteostasis in early development has significant implications for neurodegenerative diseases, particularly those involving protein aggregation, such as Parkinson's disease and Alzheimer's disease. Alpha-synuclein, a key protein implicated in synucleinopathies, is highly sensitive to disruptions in protein degradation pathways [6]. Evidence suggests that early-life impairments in autophagy or chaperone-mediated folding may facilitate the misfolding and aggregation of alpha-synuclein, setting the stage for its pathological accumulation in adulthood [10]. The process, description and implications of neurogenesis and synaptogenesis, myelination and cellular maturation and protein hemostasis in early development is summarized in table 1.

Table 1: The summary of neurogenesis and synaptogenesis, myelination and cellular maturation and protein hemostasis in early development.

Process	Description	Implications	References
Neurogenesis and Synaptogenesis	Formation of new neurons from neural stem cells, followed by their migration, differentiation, and establishment of synaptic connections. This process is guided by intrinsic genetic programs and extrinsic environmental signals.	Dysregulation may result in cognitive deficits and is linked to neurodevelopmental disorders (e.g., autism, schizophrenia). It also affects proper circuit formation, which is essential for later cognitive and motor functions.	[15-17]
Myelination and Cellular Maturation	Development of myelin sheaths around axons by oligodendrocytes, essential for rapid nerve impulse conduction. The process is regulated by signalling pathways such as Wnt, Shh, and Notch, ensuring the maturation of neural circuits.	Abnormal myelination can lead to neurodevelopmental issues (e.g., cerebral palsy, leukodystrophies) and may predispose individuals to neurodegenerative diseases later in life, including multiple sclerosis and Parkinson's disease.	[21,22,25,26]
Protein Homeostasis in Early Development	Maintenance of proper protein folding, synthesis, and degradation through mechanisms such as the ER stress response, UPR, autophagy, and molecular chaperones.	Impaired proteostasis can lead to misfolded proteins and early aggregation events (e.g., alpha-synuclein aggregation), which may prime the brain for neurodegenerative diseases such as Parkinson's and Alzheimer's in later life.	[4,6,28,31]

3. ALPHA-SYNUCLEIN AND ITS ROLE IN NEONATAL BRAIN DEVELOPMENT

Alpha-synuclein is a neuronal protein primarily localised in presynaptic terminals, where it plays a crucial role in synaptic vesicle trafficking, neurotransmitter release, and synaptic plasticity [6]. Although extensively studied in the context of neurodegenerative disorders such as Parkinson's disease, its physiological role in neonatal brain development remains underexplored. However, emerging evidence suggests that alpha-synuclein is vital for early neuronal function and circuit formation.

3.1 Alpha-Synuclein in Synaptic Development and Plasticity

Alpha-synuclein interacts with SNARE proteins, particularly synaptobrevin-2, to regulate vesicle docking and fusion at presynaptic terminals, influencing neurotransmitter release[35]. During neonatal brain development, synaptic plasticity is essential for the establishment of functional neural circuits, and alpha-synuclein has been implicated in modulating short-term synaptic dynamics [36]. Studies in alpha-synuclein knockout models have demonstrated deficits in neurotransmitter release efficiency, suggesting its necessity in early synaptic maturation [37].

3.2 Alpha-Synuclein Expression and Regulation in the Neonatal Brain

Alpha-synuclein is highly expressed in the developing brain, particularly in regions associated with motor control and cognitive functions, such as the substantia nigra and hippocampus [38]. The regulation of alpha-synuclein expression during early development is influenced by epigenetic mechanisms and extracellular signalling pathways, including oxidative stress responses and neurotrophic factors [39]. Disruptions in these regulatory processes may contribute to aberrant alpha-synuclein

accumulation, increasing vulnerability to neurodegenerative conditions later in life.

3.3 Pathological Aggregation of Alpha-Synuclein in Early Life

Under physiological conditions, alpha-synuclein exists as an intrinsically disordered protein, maintaining a dynamic equilibrium between monomeric and oligomeric states [40]. However, environmental stressors, genetic mutations, and mitochondrial dysfunction can promote the misfolding and aggregation of alpha-synuclein, forming toxic oligomers and fibrils [41]. Studies have shown that perinatal exposure to oxidative stressors or neurotoxic agents can enhance alpha-synuclein aggregation, potentially seeding neurodegenerative pathology in later life [42].

3.4 Implications for Neurodegenerative Disease Risk

The early-life misfolding of alpha-synuclein may serve as a predisposing factor for neurodegenerative diseases, particularly synucleinopathies such as Parkinson's disease and dementia with Lewy bodies. Evidence suggests that pathological alpha-synuclein aggregates formed during neonatal development may persist and propagate over time, contributing to neurotoxicity and neuronal loss in ageing individuals [10]. Understanding the mechanisms that regulate alpha-synuclein homeostasis in early brain development could provide novel insights into therapeutic strategies for neurodegenerative disorders. The aspect, description and implications of alpha-synuclein in synaptic development and plasticity, alpha-synuclein expression and regulation in the neonatal brain, pathological aggregation of alpha-synuclein in early life and the implications for neurodegenerative disease risks are summarized in table 2.

Table 2: The summary of alpha-synuclein in synaptic development and plasticity, alpha-synuclein expression and regulation in the neonatal brain, pathological aggregation of alpha-synuclein in early life and the implications for neurodegenerative disease risks.

Aspect	Description	Implications	References
Alpha-Synuclein in Synaptic Development and Plasticity	Regulates synaptic vesicle docking and fusion by interacting with SNARE proteins, influencing neurotransmitter release and synaptic plasticity.	Deficiencies in alpha-synuclein lead to impaired neurotransmitter release and synaptic dysfunction, potentially affecting early brain circuit formation.	[35-37]
Alpha-Synuclein Expression and Regulation in the Neonatal Brain	Highly expressed in the developing brain, particularly in motor and cognitive regions. Its expression is modulated by epigenetic and extracellular signaling pathways.	Dysregulation may lead to aberrant protein accumulation, increasing susceptibility to neurodegeneration in later life.	[38,39]
Pathological Aggregation of Alpha-Synuclein in Early Life	Exists in a dynamic equilibrium between monomers and oligomers. Environmental stressors, genetic mutations, and mitochondrial dysfunction promote misfolding and aggregation.	Early-life oxidative stress and neurotoxins can seed misfolded alpha-synuclein aggregates, potentially acting as precursors for later neurodegenerative disease.	[40-42]
Implications for Neurodegenerative Disease Risk	Early-life alpha-synuclein misfolding may persist and propagate, leading to neurotoxicity and neuronal loss over time.	Neonatal disruptions in alpha-synuclein homeostasis may predispose individuals to neurodegenerative diseases like Parkinson's and dementia with Lewy bodies. Understanding these processes can aid in early detection and therapeutic interventions.	[10]

4. PROTEIN AGGREGATION IN EARLY DEVELOPMENT AND NEURODEGENERATION

4.1 Mechanisms of Alpha-Synuclein Aggregation

Alpha-synuclein is an intrinsically disordered protein that can transition from its native soluble state to oligomeric and fibrillar conformations, which are implicated in neurodegenerative disorders such as Parkinson's disease[8]. The aggregation process is driven by factors such as oxidative stress, mitochondrial dysfunction, and disruptions in protein degradation pathways [43].

Oxidative stress, caused by an imbalance between reactive oxygen species and antioxidant defences, accelerates alpha-synuclein misfolding and aggregation [44]. Mitochondrial dysfunction, particularly defects in complex I of the electron

transport chain, has been linked to increased alpha-synuclein accumulation and neurotoxicity [45]. Furthermore, impairments in the UPS and autophagy-lysosomal pathways hinder the clearance of misfolded proteins, allowing toxic aggregates to persist and propagate [46].

4.2 Neonatal Triggers for Protein Misfolding

During neonatal brain development, various environmental and physiological stressors can perturb protein homeostasis, leading to early aggregation of alpha-synuclein. Perinatal hypoxia, a condition marked by oxygen deprivation during birth, has been associated with increased oxidative stress and neuronal damage, creating a permissive environment for protein misfolding [47].

Inflammation is another critical factor influencing neonatal protein aggregation. Maternal immune activation and perinatal infections elevate pro-inflammatory cytokines, such as TNF-α and IL-6, which have been shown to disrupt proteostasis and enhance alpha-synuclein aggregation [48]. Additionally, environmental toxins such as pesticides, heavy metals, and air pollutants can act as early-life stressors that prime the brain for neurodegeneration. Studies have demonstrated that neonatal exposure to rotenone, a mitochondrial toxin, increases alpha-synuclein aggregation and neuroinflammation, mirroring key pathological features of Parkinson's disease [49].

4.3 Links Between Neonatal Protein Aggregation and Adult Neurodegeneration

Epidemiological and experimental studies suggest that early-life brain insults may increase susceptibility to neurodegenerative disorders later in life. Prenatal and neonatal exposure to environmental neurotoxins, including paraquat and maneb, has been linked to an elevated risk of Parkinson's disease in adulthood [50]. These compounds induce oxidative stress and impair mitochondrial function, promoting the early aggregation of alpha-synuclein and subsequent neuronal loss.

Experimental models further support the connection between neonatal insults and adult neurodegeneration. Rodent studies have demonstrated that perinatal hypoxia results in persistent neuroinflammation and altered dopamine signalling, which are hallmark features of Parkinson's disease [51]. Similarly, neonatal exposure to bacterial endotoxins has been shown to trigger glial activation and long-term disruptions in protein homeostasis, exacerbating alpha-synuclein pathology [52]. The aspect, description and implications of mechanisms of alpha-synuclein, neonatal triggers for protein misfolding and the links between neonatal protein aggregation and adult neurodegeneration are summarized in table 3.

Table 3: The summary of mechanisms of alpha-synuclein aggregation, neonatal triggers for protein misfolding and links between neonatal protein aggregation and adult neurodegeneration.

Aspect	Description	Implications	References
Mechanisms of Alpha-Synuclein Aggregation	Alpha-synuclein transitions from a soluble state to toxic oligomeric and fibrillar forms due to oxidative stress, mitochondrial dysfunction, and impaired protein degradation.	Aggregation contributes to neurodegenerative diseases such as Parkinson's by disrupting neuronal function and triggering cell death.	[8,43,44]
Neonatal Triggers for Protein Misfolding	Perinatal hypoxia, inflammation, and exposure to neurotoxins (e.g., pesticides, heavy metals) disrupt protein homeostasis, leading to early misfolding and aggregation.	Neonatal exposure to environmental stressors increases the likelihood of neurodegenerative disease development later in life, as early protein misfolding may serve as a priming event.	[47-49]
Links Between Neonatal Protein Aggregation and Adult Neurodegeneration	Early-life stressors and protein aggregation may persist over time, predisposing individuals to neurodegenerative diseases in adulthood.	Prenatal and neonatal exposure to neurotoxins (e.g., paraquat, maneb) has been linked to increased risk of Parkinson's disease. Perinatal hypoxia and infections can lead to persistent neuroinflammation and alpha-synuclein aggregation.	[50-52]

5. IMPLICATIONS FOR NEURODEGENERATIVE DISEASES

Understanding the developmental origins of alpha-synucleinopathy is crucial for identifying early intervention strategies aimed at reducing the long-term risk of neurodegenerative diseases. Emerging evidence suggests that neonatal disruptions in protein homeostasis may serve as predisposing factors for disorders such as Parkinson's disease, dementia with Lewy bodies, and multiple system atrophy [53].

5.1 Early Biomarkers of Neonatal Protein Aggregation

Identifying biomarkers that indicate early-life protein aggregation could aid in diagnosing individuals at risk of neurodegenerative diseases before clinical symptoms appear. Recent studies have highlighted the potential of alpha-

synuclein species, including oligomeric and phosphorylated forms, as early indicators of disease progression [54]. Additionally, exosomal alpha-synuclein in cerebrospinal fluid and blood plasma has been proposed as a non-invasive biomarker reflecting early neuropathological changes [55].

Neuroinflammatory markers such as increased levels of TNF-α, IL-1β, and IL-6 in neonatal blood samples have also been associated with higher risks of developing Parkinson's disease and related disorders later in life [56]. Advances in proteomics and metabolomics may further enable the identification of molecular signatures indicative of early-stage protein misfolding and neuroinflammation [57].

5.2 Neuroprotective Strategies Targeting Protein Homeostasis

Given the role of proteostasis in neurodevelopment and disease, strategies aimed at preserving protein quality control mechanisms may offer therapeutic potential. Pharmacological approaches targeting autophagy, such as rapamycin and trehalose, have shown promise in promoting alpha-synuclein clearance and reducing neurotoxicity in preclinical models [58]. Enhancing chaperone-mediated autophagy through small-molecule activators like arimoclomol has also been explored as a potential strategy to mitigate protein aggregation [59].

Additionally, antioxidant and anti-inflammatory therapies may help counteract early oxidative stress and neuroinflammation linked to neonatal protein aggregation. Compounds such as N-acetylcysteine, resveratrol, and curcumin have demonstrated neuroprotective effects by modulating redox balance and suppressing pro-inflammatory pathways [60].

5.3 Preventative and Translational Approaches

Beyond pharmacological interventions, lifestyle modifications during pregnancy and early postnatal life may play a role in reducing the risk of neurodegenerative disorders. Maternal nutrition, avoidance of environmental toxins, and minimising perinatal hypoxic events are critical factors that could influence neonatal brain development and long-term neurological health [61].

Recent advances in gene therapy and CRISPR-based interventions also hold potential for correcting genetic predispositions to alpha-synucleinopathy. Targeting genetic variants associated with increased alpha-synuclein expression, such as SNCA gene multiplications, may provide a preventative approach for high-risk individuals [62]. The aspect, description and implications of early biomarkers of neonatal protein aggregation, neuroprotective strategies targeting protein momeostasis and preventative and translational approaches are summarized in table 4.

Table 4: The summary of early biomarkers of neonatal protein aggregation, neuroprotective strategies targeting protein momeostasis and preventative and translational approaches.

Aspect	Description	Implications	References
Early Biomarkers of Neonatal Protein Aggregation	Alpha-synuclein species (oligomeric, phosphorylated), exosomal alpha-synuclein in CSF and blood, and neuroinflammatory markers (TNF-α, IL-1β, IL-6).	Early detection of neonatal protein aggregation could help identify individuals at risk of neurodegenerative diseases before symptoms appear, allowing for earlier intervention.	[54-56]
Neuroprotective Strategies Targeting Protein Homeostasis	Pharmacological approaches (e.g., rapamycin, trehalose) enhance autophagy, while chaperone-mediated therapy (e.g., arimoclomol) improves protein clearance.	Enhancing protein degradation mechanisms may reduce alpha-synuclein aggregation and neurotoxicity, potentially mitigating the progression of neurodegenerative diseases like Parkinson's.	[58-59]
Preventative and Translational Approaches	Lifestyle factors (maternal nutrition, toxin avoidance) and advanced gene therapy (CRISPR-based interventions) to reduce genetic risk of alpha-synucleinopathy.	Preventative strategies targeting early-life factors may reduce neurodegenerative disease risk. Gene therapy holds potential for correcting genetic predispositions, preventing excessive alpha-synuclein accumulation.	[61-62]

6. FUTURE DIRECTIONS

Further research is essential to comprehensively elucidate the role of alpha-synuclein in early brain development and its potential implications for neurodegenerative diseases such as Parkinson's disease. Although alpha-synuclein is primarily studied in the context of pathological aggregation in adult neurodegeneration, emerging evidence suggests that it may play a critical role in neuronal differentiation, synaptic plasticity, and neurodevelopmental processes. Understanding these early physiological functions could provide novel insights into how dysregulation leads to disease progression later in life.

Longitudinal studies investigating neonatal protein aggregation and its long-term impact on neuronal health and adult

neurodegeneration are crucial. Prospective cohort studies tracking alpha-synuclein expression and aggregation from birth to adulthood could help establish a timeline of pathological changes. These studies could also explore genetic and environmental factors that modulate alpha-synuclein dynamics during development, potentially identifying early biomarkers of disease susceptibility.

Advancements in imaging modalities and biomarker discovery will be instrumental in detecting early pathological changes associated with alpha-synuclein abnormalities. High-resolution neuroimaging techniques, such as positron emission tomography and magnetic resonance imaging, combined with novel radiotracers, could enable the in vivo visualisation of alpha-synuclein deposition in the developing brain. Additionally, mass spectrometry-based proteomics and electrochemistry-coupled MALDI-MSI imaging may provide highly sensitive approaches for quantifying alpha-synuclein expression and aggregation at the molecular level.

Furthermore, integrating multi-omics approaches, including genomics, transcriptomics, and metabolomics, could uncover new regulatory pathways and molecular interactions influencing alpha-synuclein function across different developmental stages. The application of artificial intelligence and machine learning in analysing large-scale biomarker datasets may enhance the predictive accuracy of early diagnostic models, facilitating timely therapeutic interventions.

Ultimately, these research directions hold significant potential in bridging developmental neurobiology and neurodegeneration, paving the way for innovative strategies in early detection, prevention, and targeted therapy for Parkinson's disease and related disorders.

7. CONCLUSION

Neonatal brain development is a dynamic process that relies on precise protein regulation. Disruptions in protein homeostasis, particularly involving alpha-synuclein, may have lasting implications for neurodegenerative diseases. Investigating the developmental origins of alpha-synucleinopathy could lead to early diagnostic and therapeutic strategies, ultimately improving outcomes for individuals at risk of neurodegenerative disorders. Further research into the mechanisms regulating neonatal proteostasis and their long-term effects on neuronal health is essential for advancing preventative and therapeutic interventions for synucleinopathies and related diseases.

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Conflict of Interest Statement:

The authors have no conflict of interest to declare.

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