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Perspective

Down Syndrome as a Model of Premature Brain Aging and Alzheimer-Type Neurodegeneration: Molecular Mechanisms and Emerging Therapeutic Perspectives

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ABSTRACT

Down syndrome (DS), caused by trisomy 21, is the most common genetic cause of intellectual disability. Improvements in medical care have markedly increased life expectancy, revealing a high prevalence of premature brain aging and Alzheimer-type neurodegeneration in adulthood. Nearly all adults with DS develop cerebral amyloid pathology by midlife, primarily due to overexpression of the amyloid precursor protein gene located on chromosome 21. However, the clinical expression of dementia is heterogeneous, indicating that additional genetic, cellular and environmental modifiers influence disease onset and progression.

This narrative review examines the molecular and cellular mechanisms contributing to early brain aging in DS, with a particular focus on Alzheimer-type pathology. We discuss gene dosage effects, dosage-sensitive genes involved in synaptic and endo-lysosomal dysfunction and the challenges associated with diagnosing dementia in individuals with pre-existing intellectual disability. Emphasis is placed on endo-lysosomal alterations as early cellular biomarkers and on recent experimental and clinical evidence implicating gonadotropin-releasing hormone (GnRH) dysfunction in cognitive impairment.

Emerging data indicate that restoration of physiological GnRH signaling may improve cognitive function and functional brain connectivity in adults with DS. Understanding DS as a genetically determined condition conferring high risk for Alzheimer-type pathology provides a unique framework for identifying early biomarkers and developing disease-modifying strategies relevant to premature aging and neurodegeneration.

Keywords: Down syndrome, Trisomy 21, Alzheimer's disease, Premature brain aging, Endo-lysosomal dysfunction, Amyloid pathology, GnRH, Cognitive decline

1. Introduction

Down syndrome (DS), resulting from trisomy 21, affects more than five million individuals worldwide and represents the leading genetic cause of intellectual disability[1]. The triplication of chromosome 21 disrupts neurodevelopment, synaptic plasticity and cognitive function from early life. With increased longevity, a second major neurological phenotype has emerged: an exceptionally high risk of Alzheimer-type neurodegeneration in adulthood[2].

By the fourth decade of life, most individuals with DS exhibit cerebral amyloid deposition, reflecting lifelong overexpression of the amyloid precursor protein (APP) gene located on chromosome 21. Nevertheless, the onset and severity of dementia vary considerably, suggesting that amyloid pathology alone is insufficient to account for cognitive decline[3]. This variability highlights the contribution of additional dosage-sensitive genes, compensatory mechanisms, cellular vulnerability and environmental influences.

This review focuses on the biological mechanisms underlying premature brain aging in DS, emphasizing Alzheimer-type pathology, early cellular biomarkers and emerging neuroendocrine mechanisms with therapeutic potential.

2. Genetic Contributors beyond APP

Although APP overexpression plays a central role in amyloid accumulation, chromosome 21 contains numerous genes whose altered dosage contributes to synaptic dysfunction, neurodevelopmental abnormalities and neuronal vulnerability. Transcriptomic studies indicate that only a subset of trisomy genes are overexpressed, reflecting compensatory regulatory mechanisms[4].

Among dosage-sensitive candidates, DYRK1A, SYNJ1, DSCAM, SIM2, OLIG1/2 and GIRK2 have been implicated in synaptic transmission, neuronal maturation and intracellular trafficking. Rather than a single causative gene, the DS phenotype likely results from the combined effects of multiple modest perturbations that accumulate across the lifespan and predispose the brain to early neurodegeneration[5].

3. Alzheimer-type Neurodegeneration in Down syndrome

Individuals with DS represent one of the populations at highest risk for Alzheimer's disease, second only to autosomal dominant familial forms. Neuropathological hallmarks, including amyloid plaques and neurofibrillary tangles, are highly prevalent with age[6]. However, the presence of pathology does not uniformly translate into dementia, underscoring the dissociation between neuropathology and clinical expression. DS should therefore be viewed not as an inevitable or uniform model of Alzheimer's disease, but as a genetically defined condition conferring exceptionally high vulnerability to Alzheimer-type pathology[7]. Differences in cognitive reserve, mutation burden, gene regulation and comorbidities likely shape clinical outcomes.

4. Endo-Lysosomal Dysfunction as an Early Biomarker

Alterations of the endo-lysosomal system constitute one of the earliest detectable cellular abnormalities in both DS and Alzheimer's disease[8]. Enlarged early endosomes have been identified in neurons and peripheral cells from individuals with DS well before the appearance of amyloid plaques. These compartments play a critical role in APP processing and their enlargement is associated with increased amyloidogenic cleavage[9].

Importantly, endo-lysosomal abnormalities are also detectable in peripheral blood cells and fibroblasts, supporting their potential use as accessible biomarkers of disease progression. The overexpression of SYNJ1, a chromosome 21 gene involved in phosphoinositide metabolism and vesicular trafficking, has been directly linked to these alterations, reinforcing the mechanistic connection between trisomy 21 and early cellular dysfunction[10].

5. GnRH Dysfunction and Cognition: A Translational Opportunity

Among emerging mechanisms, dysfunction of the gonadotropin-releasing hormone (GnRH) system represents one of the most compelling and experimentally supported contributors to cognitive impairment in DS. In addition to its reproductive role, GnRH neurons project to brain regions involved in cognition, including the hippocampus and cortex.

In the Ts65Dn mouse model, progressive reductions in GnRH expression are associated with olfactory deficits, impaired synaptic transmission and cognitive decline. These alterations originate early in development and precede overt neurodegeneration. Restoration of physiological GnRH signaling via genetic, pharmacological or cell-based approaches-rescues cognitive performance, hippocampal activity and synaptic function, even when initiated in adulthood.

Crucially, a pilot clinical study in adult men with DS demonstrated that six months of pulsatile GnRH administration improved cognitive performance and normalized resting-state functional connectivity in key neural circuits. These findings identify GnRH dysfunction as a modifiable neuroendocrine mechanism linking trisomy 21 to premature brain aging[11].

5. Conclusion

Down syndrome is associated with premature brain aging and a markedly increased risk of Alzheimer-type neurodegeneration. While lifelong gene overexpression on chromosome 21 creates a strong biological predisposition, the clinical expression of dementia is heterogeneous and influenced by multiple modifiers. Recent advances have identified early cellular biomarkers, including endo-lysosomal dysfunction and uncovered neuroendocrine mechanisms that actively contribute to cognitive decline. Among these, impaired GnRH signaling emerges as a particularly promising therapeutic target, supported by converging evidence from animal models and preliminary clinical studies. Future research should prioritize early identification of at-risk individuals and rigorously designed clinical trials aimed at preserving cognitive function and quality of life in adults with Down syndrome.

6. References

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