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Review Article

Advancements in understanding and addressing Alzheimer's disease: a comprehensive review

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ABSTRACT

Alzheimer's disease (AD) presents a multifaceted challenge in the realm of neurodegenerative disorders, affecting millions globally and posing significant burdens on patients, caregivers, and healthcare systems alike. Over a century of research has illuminated various facets of AD pathophysiology, highlighting the intricate interplay between genetic, molecular, and environmental factors in disease progression. This comprehensive review synthesized key findings from recent literature, encompassing diverse topics ranging from diagnostic challenges and emerging therapeutic approaches to caregiver support and evolving research strategies. Furthermore, it explored the complexities of AD pathogenesis, elucidating the role of amyloid-beta (Aβ) plaques, tau protein pathology, neuroinflammation, and mitochondrial dysfunction in neuronal degeneration. Therapeutic interventions for AD, both current and emerging, are critically evaluated, with a focus on pharmacological agents targeting Aβ aggregation, tau pathology, and synaptic dysfunction. Non-pharmacological strategies, including lifestyle modifications and cognitive interventions, are also explored for their potential in disease management. Finally, the review examined the landscape of AD research, highlighting ongoing efforts to elucidate disease mechanisms, identify novel therapeutic targets, and address existing gaps in prevention and treatment strategies. It emphasizes the need for collaborative endeavours among stakeholders to accelerate progress towards effective AD management and ultimately, improve outcomes for affected individuals and their families. Through its comprehensive synthesis of current knowledge and future directions, this review aims to inform clinicians, researchers, policymakers, and advocates involved in the fight against Alzheimer's disease, offering insights that may catalyse advancements in diagnosis, treatment, and care.

Keywords: Alzheimer’s disease, Beta-amyloid plaques, Biomarkers, National Institute on aging-alzheimer’s association

INTRODUCTION

Alzheimer’s disease (AD) emerges as a significant topic within the realm of dementia research, shedding light on the intricate interplay between neurophysiological abnormalities and cognitive dysfunction. With over a century of investigation since its initial documentation in 1906, a multitude of genetic and molecular pathways driving the progression of AD have been unraveled, extending beyond traditional neuropathological markers like beta-amyloid plaques and neurofibrillary tangles. This extensive review synthesized key findings linking neurodegeneration in AD to its clinical presentation and therapeutic modalities, emphasizing the complex and interconnected nature of disease pathophysiology. Moreover, it provided valuable insights into diagnostic protocols based on the clinical recommendations outlined by the National Institute on aging-alzheimer’s association (NIA-AA) workgroup. By disseminating accessible resources such as this review, endeavours were made to enhance educational equity and accessibility, particularly for contemporary clinicians seeking comprehensive

understanding and effective management strategies for AD.[1] AD is characterized by cognitive decline, neurodegeneration, and the presence of Aβ-plaques and neurofibrillary tangles. The pathogenesis of AD involves the complex interplay of Aβ and tau proteins, as well as the involvement of glial cells in various molecular and cellular pathways. Risk factors associated with AD include genetics, aging, environmental variables, lifestyle habits, medical conditions, viral/bacterial infections, and psychiatric factors. The ubiquitin-proteasome pathway (UPP) plays a crucial role in maintaining cellular integrity and removing toxic and improperly folded proteins. Disruption of this pathway leads to the accumulation of aberrant protein complexes in brain cells, which is thought to be a pathogenic characteristic of AD. Aging is the primary risk factor for AD, with the majority of cases occurring after the age of 65. Aging leads to reduced brain size, synaptic loss, and the accumulation of amyloid plaques and neurofibrillary tangles. Other factors such as glucose hypometabolism, cholesterol dysregulation, mitochondrial dysfunction, depression, and cognitive impairment may also be associated with AD and complicate its diagnosis.[2]

AD stands as a prevalent neurological challenge marked by memory loss, cognitive decline, and eventual dementia, disproportionately afflicting individuals aged 65 and beyond. Its symptomatic spectrum spans from early pre-dementia stages to debilitating dementia, presenting a complex clinical landscape. The underlying pathogenesis implicates the accumulation of toxic amyloid-β plaques (Aβ) and hyperphosphorylated tau (p-tau), unravelling the intricate molecular mechanisms at play. Notably, risk factors for late-onset Alzheimer's encompass a blend of immutable factors like age and genetics alongside modifiable elements such as cardiovascular health, lifestyle patterns, and environmental influences. The diagnostic paradigm has evolved significantly, propelled by advancements in genetics, the emergence of biomarkers indicative of neurodegeneration, and the refinement of neuroimaging modalities. Treatment modalities for AD presently entail acetylcholinesterase inhibitors and N-methyl D-aspartate antagonists, supplemented by a diverse pipeline of investigational drugs undergoing rigorous clinical evaluation to broaden therapeutic options.[3] AD presents as a complex neurodegenerative condition marked by impairments in memory, executive function, and visuospatial abilities. Effective management strategies necessitate a comprehensive approach, emphasizing collaboration with patients and their families, alongside meticulous psychiatric, neurological, and general medical assessments to address cognitive deficits and associated symptoms. Pharmacological interventions, currently comprising three cholinesterase inhibitors and one N-methyl-D-aspartate (NMDA) antagonist, serve as pivotal components of AD treatment, either independently or in combination. Cholinesterase inhibitors emerge as the primary therapeutic choice for individuals with mild to moderate AD, potentially mitigating symptomatic cognitive and functional decline. Additionally, memantine stands as a viable alternative, either as monotherapy or in conjunction with cholinesterase inhibitors, offering symptomatic relief. Nonetheless, it's crucial to note that these pharmacotherapeutic options do not alter the course of disease progression.[4]

UNDERSTANDING AD

AD affects approximately 50 million individuals globally, making it the leading cause of dementia, accounting for about 70% of cases. Its pathophysiology involves the accumulation of amyloid plaques and tau tangles in the brain, leading to neuronal damage and cognitive decline. The disease progresses through stages, from a preclinical phase to mild cognitive impairment (MCI), culminating in clinical dementia. Diagnosis now relies on biomarkers reflecting amyloid and tau pathology, such as CSF levels of amyloid-beta 1-42, phosphorylated tau, and total tau. Despite numerous clinical trials targeting these proteins, no disease-modifying treatments are available, highlighting the complexity of AD pathophysiology. Biological heterogeneity within AD poses a challenge to treatment development, with studies revealing subgroups based on CSF tau levels and conflicting findings in proteomic analyses. Factors like APOE ε4 carriership, age, and sex influence CSF protein levels and contribute to understanding early AD pathogenesis. Memory dysfunction, a hallmark of AD, is linked to synaptic loss, yet the timing of synaptic changes remains unclear. This review article explores the use of CSF proteomic techniques to investigate AD subgroups and related processes, aiming to advance our understanding of the disease's heterogeneity and inform potential therapeutic strategies.[5] AD stands as the primary cause of dementia worldwide, characterized by the presence of beta-amyloid plaques, neurofibrillary tangles, and neuroinflammation in its pathology. In contrast to traditional diagnostic approaches based on clinical criteria, modern methods hinge on biomarkers imaging and fluid tests. Presently, treatment strategies for AD predominantly address symptomatic relief. However, ongoing research is actively exploring advanced therapies directed at targeting AD hallmarks, including anti-beta-amyloid and APOE-related treatments.[6]

AD presents a significant global challenge, particularly affecting individuals aged 65 years and older and standing as the foremost cause of dementia. The prevalence, incidence, and mortality rates associated with AD are on the rise, partially attributed to underdiagnosis. MCI stemming from AD frequently progresses to AD dementia, with estimates of AD dementia aetiology among MCI patients ranging from 40% to 75%. The risk of AD dementia escalates with the transition from normal cognition to early neurodegeneration and MCI. Among individuals with Aβ accumulation and neurodegeneration, the lifetime risk of AD dementia is estimated at 41.9% for women and 33.6% for men. Although data on the

progression from preclinical AD to MCI are limited, NIA-AA stage 3 (characterized by subtle cognitive decline with AD biomarker positivity) may offer insights for treatment decisions. Risk factors for AD dementia encompass a lower MMSE score, higher ADAS-cog score, positive APOE4 status, white matter hyperintensities volume, entorhinal cortex atrophy, CSF total tau, CSF neurogranin levels, dependency in IADL, and female gender. The integration of biomarkers with neurocognitive tests is anticipated to hold pivotal significance in clinical practice, particularly with the advent of novel disease-modifying therapies.[7]

INSIGHT INTO AD

AD represents a significant challenge in healthcare due to its progressive nature, leading to debilitating dementia and ultimately, mortality. Pathologically, AD is characterized by the presence of intracellular neurofibrillary tangles and extracellular amyloid beta (Aβ) plaque accumulation, accompanied by neurodegeneration. A myriad of factors contributes to the progression of AD, ranging from genetic mutations to neuroinflammation, blood-brain barrier (BBB) dysfunction, mitochondrial impairment, oxidative stress, and dysregulation of metal ions. Recent investigations have shed light on the involvement of altered hem metabolism in AD pathogenesis, adding to the complexity of its aetiology. Despite extensive research efforts spanning decades, the lack of effective treatments underscores the urgency of comprehending the underlying cellular and molecular mechanisms driving AD pathology. This review delves into promising therapeutic targets essential for advancing AD drug discovery, while also emphasizing the pivotal role of hem in disease development. Additionally, it provides insights into mathematical models, including stochastic approaches and those delineating the impact of Aβ, offering potential treatment avenues for evaluation in clinical trials.[8]

AD presents considerable obstacles for both researchers and healthcare professionals due to its intricate pathology and the absence of viable treatment options. Ongoing research endeavours seek to consolidate existing knowledge regarding the disease and provide guidance for future investigations aimed at developing effective therapies. This involves a thorough analysis of data extracted from academic literature, coupled with an exploration of pertinent theories such as the amyloid cascade hypothesis. Proposed areas for future research encompass delving into the underlying causes of protein abnormalities, exploring treatments targeting tau pathology, and elucidating the correlation between maintaining a healthy lifestyle and preserving cognitive function.[9] AD, a prevalent neurodegenerative disorder predominantly affecting the elderly population, manifests through cognitive decline, memory impairment, and behavioural changes. Its pathophysiology involves a complex interplay of various factors including excitotoxicity, cholinergic dysfunctions, oxidative stress, tau protein hyperphosphorylation, alterations in amyloid-beta peptide metabolism, herpes viruses, apolipoprotein E, glycogen synthase kinase 3, insulin resistance, and the endocannabinoid system. Extensive literature has explored therapeutic interventions targeting these pathogenic mechanisms to alleviate the clinical manifestations of the disease. A comprehensive review was undertaken to elucidate the molecular underpinnings of these pathophysiological hypotheses, to deepen our understanding and potentially pave the way for novel pharmacological strategies in the management of AD.[10]

DIAGNOSTIC CHALLENGES AND ADVANCES

Detection of neurodegenerative diseases in their early stages has been challenging, with limited success thus far. The article delves into the biochemical characteristics of AD along with the existing methods for its detection. It also assesses the accuracy, invasiveness, and time requirements of current AD detection techniques. Furthermore, there is a discussion on innovative approaches for detecting other neurodegenerative diseases and how these methodologies could potentially be adapted for early detection of AD. Additionally, the article provides a detailed explanation of a diagnostic test grounded in the discussed detection principles, alongside proposing a theoretical creation of a fluorescent assay as a potential method for detecting AD.[11]

AD is a progressive neurodegenerative disorder that affects millions of people worldwide and is characterized by various pathological changes, including blood-brain barrier disruption, oxidative stress, mitochondrial impairment, neuroinflammation, and hypometabolism. The pathological changes associated with AD may begin several years before clinically detectable disease, suggesting that pharmacological therapy in the pre-clinical stage could be beneficial. Early diagnosis techniques, such as cerebrospinal fluid biomarkers and amyloid positron emission tomography neuroimaging, are crucial for testing potential disease-modifying therapies in clinical trials. Recent trials of agents like aducanumab have shown promising results in potentially delaying the onset of dementia and reducing its prevalence, but caution is needed in interpreting these findings.[12]

AD is a major neurodegenerative condition with a long history of being a significant concern due to its fatal consequences. Current treatments primarily aim at alleviating symptoms as there are few curative options available. Consequently, there's a growing emphasis on early diagnosis as it plays a critical role in both prevention and treatment strategies, garnering considerable attention in research endeavours. Despite the development of diverse molecular diagnostic probes, which have shown promising outcomes in mouse models, validating their efficacy in human brains remains a significant challenge.[13]

TREATMENT STRATEGIES AND THERAPEUTIC APPROACHES

AD is a progressive neurodegenerative disorder of the central nervous system and the leading cause of dementia in elder people. The clinical symptoms of AD are memory loss and cognitive dysfunction. AD is characterized by the deposition of β-amyloid plaques and neurofibrillary tangles of hyperphosphorylated tau protein in the brain and neurodegeneration. The cause of AD is not known, but various genetic and non-genetic factors have been involved in the pathogenesis. The main genetic risk factor of AD is the E4 allele of apolipoprotein E. Currently, no effective treatment is available for AD. Only two classes of drugs, acetylcholinesterase inhibitors (galantamine, rivastigmine, donepezil), and N-methyl-D-aspartate receptor antagonist (memantine), are available for AD treatment, but they have limited effectiveness and disagreeable side-effects. Various diagnostic and prognostic biomarkers have been identified for the management of AD, which can help in early detection, monitoring disease progression, and assessing treatment response.[14] AD represents the most common form of dementia among the elderly, characterized by progressive decline in memory and cognitive function. Current therapeutic efforts are primarily directed towards inhibiting the synthesis and aggregation of beta-amyloid and tau proteins, both hallmark features of AD pathology. While early therapeutic agents focused on compensating for cholinergic neuron loss, such as cholinesterase inhibitors, they only offer symptomatic relief without halting disease progression. Recent decades have witnessed significant advancements in understanding the molecular and cellular changes underlying AD pathology. The etiology of AD is multifaceted, with sporadic cases arising from unknown causes and a smaller portion linked to familial inheritance, often associated with mutations in genes like APP, PS1, and PS2. Ongoing research explores novel therapeutic avenues, including next-generation AChE and BChE inhibitors undergoing clinical evaluation for symptomatic relief. Additional strategies for slowing AD progression encompass serotonergic modulation, H3 receptor antagonism, phosphodiesterase inhibition, COX-2 inhibition, and MAO-B inhibition. This comprehensive review delves into potential therapeutic approaches and their underlying molecular mechanisms, offering insights into both traditional and future strategies for managing AD.[15]

Cognitive impairment poses a significant challenge in bipolar disorder, impeding recovery and reducing overall quality of life. Currently, there is a lack of definitive treatments addressing cognitive impairment in bipolar disorder, prompting exploration into various pharmacological interventions. These interventions encompass traditional treatments such as lithium, lamotrigine, aripiprazole, asenapine, cariprazine, lurasidone, olanzapine, vortioxetine, fluoxetine, tianeptine, and modafinil, alongside emerging options like galantamine, donepezil, pramipexole, erythropoietin, mifepristone, infliximab, minocycline, doxycycline, ketamine, insulin, metformin, liraglutide, probiotic supplements, and *Withania somnifera*. However, the investigation of interventions for cognitive impairment in bipolar disorder remains relatively under-researched, with historical methodological pitfalls in cognition trials serving as significant limitations. There is a pressing need to expand the existing literature and identify novel pharmacological and non-pharmacological approaches to address cognitive impairment in bipolar disorder effectively.[16]

CAREGIVER CHALLENGES AND SUPPORT

Caregiving for older relatives has become common and stressful due to increased life expectancy. AD and related disorders pose particular challenges for caregivers due to behavioural and affective symptoms or severe disability. Interventions identified in the literature can reduce burden and improve emotional well-being for caregivers. Support from family, friends, and paid help can alleviate stress and improve well-being for caregivers. Despite research showing potential for reducing stress and burden, many caregivers receive minimal or no help.[17] Caregiving for Alzheimer's patients, particularly those residing at home, poses significant challenges. In a study involving eight caregivers utilizing a case study approach, researchers sought insights into the burdens and difficulties they encountered. Findings revealed that caregivers grapple with daily hurdles encompassing physical and psychological health issues, limited social support and resources, familial discord, crises, and criticism. Moreover, caregivers navigate both positive and negative aspects within their roles, often turning to religiosity for solace. Consequently, the study underscores the necessity for tailored programs and interventions addressing the multifaceted challenges encountered by Alzheimer's caregivers to foster constructive social change.[18]

The qualitative study conducted in Iran in 2020 aimed to explore the experiences of family caregivers in providing care to Alzheimer's patients. Through in-depth and semi-structured interviews with 11 caregivers, the researchers identified two main categories: burnout and exhaustion and excellence and personal growth. Caregivers expressed both positive and negative dimensions of caregiving for AD patients, highlighting challenges such as caregiving strain and the progressive nature of the disease. It underscores the importance for health planners to address caregivers' challenges and provide appropriate support strategies.[19] Caregivers of patients with AD experience considerable burden and challenges due to the gradual decline in cognition, language, and memory in patients, which affects daily functioning. Their pivotal role in assisting patients often leads to strain, as evidenced by the substantial time spent by informal caregivers in 2018. This strain may result in caregivers neglecting their own self-care needs and withdrawing

from social interactions. Common challenges faced by AD caregivers encompass limited social engagement, concerns regarding sexuality, and sleep disturbances. Recognizing these challenges can enable nurses and healthcare professionals to provide better support to families through proactive measures. Essential investment in resources is necessary to enhance the physical and mental well-being of caregivers. Additionally, further research is imperative to address the knowledge gaps identified in the literature review concerning this subject.[20]

EMERGING RESEARCH AND EVOLVING STRATEGIES

This review article provides a comprehensive examination of the diverse array of pharmacological and non-pharmacological interventions for AD, ranging from established treatments to emerging therapeutic strategies. It meticulously explores the implications of these interventions for both AD patients and their families, shedding light on the potential broader societal impact of advancements in treatment options. Furthermore, the article critically analyses the challenges and opportunities inherent in the design of clinical trials, as well as the regulatory and ethical considerations surrounding novel treatments. It also offers insights into future directions for AD treatment, highlighting the promise of personalized medicine and combination therapies. Despite recognizing the obstacles posed by clinical trial design, regulatory frameworks, public health policies, and funding constraints, the article underscores the imperative for collaborative efforts among stakeholders—including healthcare providers, researchers, policymakers, and advocates-to realize meaningful improvements in care and outcomes for individuals living with AD.[21] AD guidelines were reviewed, revealing limited consensus on diagnostic practices and treatment strategies. Notable findings include discouragement of asymptomatic screening, lack of agreement on neurocognitive assessment tools, and unsupported pharmacological interventions for MCI. While pre- and post-2018 guidelines aligned on screening and treatment, guidance on forthcoming disease-modifying treatments (DMTs) is lacking. Regular updates are essential to integrate evolving technologies and advance precision medicine in AD management.[22]

AD presents significant challenges in neurological care, primarily impacting cognitive function in the elderly. Various hypotheses, including amyloid β (Aβ) accumulation and tau protein aggregation, have inspired diverse therapeutic approaches. Yet, current pharmacological interventions only offer symptomatic relief. Overcoming the BBB remains a critical hurdle, but nanoparticles show promise in facilitating targeted drug delivery. Natural compounds like alkaloids and flavonoids exhibit potential in preclinical studies. Computational techniques expedite drug discovery, signalling a hopeful trend towards novel therapies aimed at improving patient well-being.[23] AD is a chronic neurological disorder leading to dementia, marked by cognitive decline, personality changes, and speech impairment. It stems from neuronal injury in specific brain regions, characterized by intraneuronal fibrillary tangles, amyloid plaque accumulation, cholinergic neuron loss, and reduced choline acetyltransferase levels. While AD remains incurable, its progression can be slowed using FDA-approved drugs like rivastigmine, galantamine, donepezil, and memantine, targeting cholinesterase and NDMA receptors. Preventative strategies encompass a holistic approach involving phytopharmaceuticals, nanomedicines, nutraceuticals, and gene therapy, with ongoing clinical trials exploring innovative treatments. Research endeavours concentrate on understanding AD pathophysiology, identifying therapeutic targets, and assessing both approved medications and novel compounds in trials, aiming to offer insights into current advancements and treatment possibilities for AD.[24]

AD represents a significant global public health challenge, particularly affecting the elderly population. The increasing life expectancy resulting from medical advancements is believed to contribute to the growing prevalence of AD. Stakeholders express concerns regarding the pace of AD research progress and the need to address existing gaps in prevention and treatment strategies. Although there has been an increase in funding for AD research in the United States, economic burdens persist. Controversies surrounding gene modification in AD treatment add complexity to research efforts. The quest for a definitive AD treatment continues amidst uncertainties regarding the safety and efficacy of recently approved drugs like Aducanumab. While newer therapies hold promise, their approval and real-world effectiveness remain pending.[25]

DISCUSSION

AD stands as a multifaceted challenge within the landscape of neurodegenerative disorders, characterized by its progressive nature and devastating impact on cognitive function. The culmination of over a century of research has unraveled intricate molecular pathways underlying AD pathogenesis, emphasizing the role of amyloid plaques, tau protein abnormalities, and neuroinflammation in driving neuronal damage and cognitive decline.

Pathophysiological insights and therapeutic implications

The amalgamation of genetic predispositions, environmental factors, and lifestyle habits underscores the complexity of AD aetiology, necessitating a holistic approach to disease management. While pharmacological interventions like acetylcholinesterase inhibitors and N-methyl-D-aspartate antagonists offer symptomatic relief, the pursuit of disease-modifying therapies remains

paramount. Recent advancements in drug discovery, including next-generation AChE and BChE inhibitors, hold promise for addressing the underlying molecular mechanisms driving AD pathology.[7-9]

Diagnostic challenges and emerging technologies

The evolution of diagnostic protocols, marked by the integration of biomarkers reflecting amyloid and tau pathology, represents a paradigm shift in early detection and disease monitoring. However, challenges persist in translating these advancements into clinical practice, particularly concerning the invasiveness and accessibility of diagnostic techniques. Innovative approaches, such as cerebrospinal fluid biomarkers and amyloid positron emission tomography neuroimaging, offer potential avenues for early intervention and therapeutic efficacy assessment.[11-13]

Caregiver burden and support strategies

The caregiving journey for individuals with AD presents profound challenges, encompassing physical, emotional, and financial burdens on caregivers. Tailored interventions aimed at alleviating caregiver strain and promoting well-being are imperative, necessitating collaborative efforts among healthcare providers, policymakers, and community stakeholders. Addressing the diverse needs of caregivers through support programs and respite services is essential in fostering sustainable caregiving environments.[17-20]

Future directions and research endeavours

As the pursuit of effective AD treatments continues, emphasis must be placed on collaborative research endeavours, regulatory frameworks, and funding initiatives to accelerate progress in disease management. Integrating emerging technologies, such as nanoparticles for targeted drug delivery and computational techniques for drug discovery, holds promise in expanding therapeutic options and improving patient outcomes. Moreover, ongoing dialogue and knowledge exchange among stakeholders is critical in addressing existing gaps in prevention, diagnosis, and treatment strategies for AD.[21-24]

CONCLUSION

AD represents a multifaceted neurological challenge with significant implications for individuals, families, and society as a whole. Over the past century, extensive research has unraveled the intricate molecular and cellular mechanisms underlying AD pathogenesis, highlighting the roles of beta-amyloid plaques, tau protein pathology, neuroinflammation, and genetic predispositions. Despite these advances, effective disease-modifying treatments remain elusive, underscoring the complexity and heterogeneity of AD. Current diagnostic protocols, incorporating biomarkers and neuroimaging techniques, offer promise in early detection and monitoring of disease progression. However, challenges persist in translating these advancements into routine clinical practice, particularly in resource-limited settings. Furthermore, caregiver burden emerges as a critical issue, necessitating tailored support programs to address the physical, emotional, and social needs of caregivers. While existing pharmacological interventions provide symptomatic relief, ongoing research efforts explore novel therapeutic targets and treatment modalities. From nanoparticles facilitating targeted drug delivery to natural compounds showing potential in preclinical studies, the landscape of AD therapeutics is evolving rapidly. Collaboration among stakeholders, including researchers, healthcare providers, policymakers, and caregivers, is crucial in advancing AD research and improving care outcomes. In the face of uncertainties surrounding recent drug approvals and controversies in gene modification therapies, the quest for effective AD treatments persists. Continued investment in research, coupled with an emphasis on personalized medicine and combination therapies, holds promise in the pursuit of meaningful advancements in AD management. Despite the challenges ahead, the collective efforts of the scientific community offer hope for a future where the burden of AD is alleviated, and individuals affected by this devastating condition can live with dignity and quality of life.

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