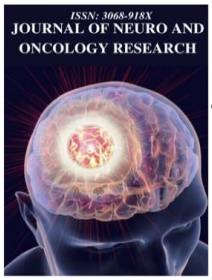

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Review Article

Alzheimer's Disease (AD) and Autism Spectrum Disorder (ASD) Comparison in Review

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Abstract

Autism Spectrum Disorder (ASD), especially with co-occurring Intellectual Disability (ID), is associated with significantly increased dementia risk. There is a notable tendency toward early-onset Alzheimer's disease. These findings support a lifespan neurobiological model, linking early neurodevelopmental disruption to later neurodegeneration.

Beyond early-life manifestations, accumulating epidemiological evidence suggests that Autism Spectrum Disorder (ASD) may confer long-term risk for neurodegenerative disorders, particularly Alzheimer's Disease (AD) and related dementias. A population-based cohort study by Diamandis, et al., reported that individuals with autism Spectrum Disorder (ASD) exhibit a significantly elevated risk of dementia, with those who also have ID demonstrating nearly threefold increased risk compared to the general population. Furthermore, individuals with Autism Spectrum Disorder (ASD) and Intellectual Disability (ID) were more likely to develop early-onset dementia, indicating a potentially accelerated trajectory of neurodegeneration. These findings suggest that neurodevelopmental disruptions in Autism Spectrum Disorder (ASD) may predispose individuals to later-life cognitive decline, particularly when compounded by intellectual impairment. Phillips (2026) proposed that impaired cerebrospinal fluid drainage may be a unifying mechanism linking Autism Spectrum Disorder (ASD)and Alzheimer's Disease (AD, whereby reduced clearance efficiency contributes to neuroinflammation, synaptic dysfunction and eventual neurodegeneration.

Review: Converging Evidence Between autism spectrum disorder and Alzheimer's Disease. Effect of Alzheimer's disease medications on neurocognitive outcomes in children and adolescents with autism spectrum disorder and low IQ: A scoping review. Prevalence of Dementia Among US Adults with Autism Spectrum Disorder. What Is Autism Spectrum Disorder? Pathophysiologic similarities between autism spectrum disorder and Alzheimer's disease. Alzheimer's disease: a comprehensive review of epidemiology, risk factors, symptoms, diagnosis, management, caregiving, advanced treatments and associated challenges. From aberrant neurodevelopment to neurodegeneration: Insights into the hub gene associated with autism and Alzheimer's disease.

Keywords: Autism Spectrum Disorder; Intellectual Disability; Alzheimer's Disease

Introduction

A large-scale cohort study published in JAMA Network Open by Vivanti, et al., examined dementia prevalence among U.S. adults with ASD using Medicare and Medicaid datasets encompassing over 100,000 individuals [1]. The findings demonstrated that dementia diagnoses were substantially more prevalent in adults with ASD compared to the general population, with approximately 8-9% of autistic adults diagnosed with dementia overall. Notably, prevalence increased dramatically with age, reaching over 30% among individuals aged 64 years and older, far exceeding rates observed in neurotypical populations.

Research on neuropsychiatric conditions within the literature review demonstrates that altered brain development, genetic susceptibility and comorbid neurological conditions frequently co-occur, reinforcing the concept of continuity between neurodevelopmental and neurodegenerative disease pathways [2].

Autism Spectrum Disorder (ASD) is a heterogeneous neurodevelopmental condition characterized by deficits in social communication and restricted, repetitive behaviors, frequently accompanied by Intellectual Disability (ID). Increasingly, research has highlighted the genetic complexity of ASD, particularly in individuals with co-occurring ID.

Over recent decades, both Autism Spectrum Disorder (ASD) and Alzheimer's disease (AD) have shown a marked increase in incidence globally. In the United States, 2022 estimates indicate ASD affects approximately 1 in 54 children, reflecting a substantial rise compared to earlier reports. Concurrently, the global burden of AD continues to expand, largely driven by population aging, with incidence increasing by approximately 147.9% between 1991 and 2019 and a current prevalence of 55 million individuals worldwide.

Autism Spectrum Disorder (ASD) typically presents within the first two years of life, with early manifestations primarily affecting social communication and behavioral patterns. Infants and toddlers with ASD often demonstrate reduced social responsiveness, including failure to respond to their name and limited use of communicative gestures such as pointing or waving. Deficits in joint attention and eye contact are also commonly observed, reflecting early disruptions in social engagement [3].

Language development may be delayed or atypical, with some children exhibiting echolalia (repetition of words or phrases) or limited functional speech. In addition, children with ASD frequently display restricted and repetitive behaviors, including motor stereotypies such as hand flapping, rocking or spinning [3]. A lack of imaginative or pretend play further distinguishes early developmental trajectories from typical patterns.

These early signs are consistent with the diagnostic criteria outlined in the Diagnostic and Statistical Manual of Mental Disorders (DSM-5-TR) and are widely supported by longitudinal developmental research which emphasizes the importance of early identification and intervention [3].

A review of the literature found many of the signs and symptoms observed in AD to be common to ASD. These similarities include increased accumulation of beta-amyloid in the brain, increased extracellular CSF, Enlarged Perivascular Spaces (EPVS), olfactory dysfunction, hypertension, increased Body Mass Index (BMI), hyperlipidemia and sleep disorders [4].

Findings

Epidemiological evidence indicates that individuals with Autism Spectrum Disorder (ASD), particularly those with co-occurring Intellectual Disability (ID), face a significantly elevated risk of Alzheimer's Disease (AD) and related dementias, with studies reporting nearly a threefold increase in risk and a higher likelihood of early-onset dementia relative to both the general population and ASD individuals without ID [5]. "Adults with ASD had a significantly increased risk of early-onset dementia compared to the general population" [5].

Pharmacological management differs markedly between AD and ASD. AD has multiple FDA-approved treatments targeting cognitive decline, including cholinesterase inhibitors (e.g., donepezil, galantamine, rivastigmine) and NMDA receptor antagonists (memantine), as well as newer monoclonal antibodies (e.g., aducanumab, lecanemab, donanemab) that reduce β-amyloid pathology. In contrast, ASD pharmacotherapy remains limited to the management of irritability, with risperidone and aripiprazole as the only approved agents and no medications are currently indicated for core cognitive deficits [5].

Emerging evidence from a scoping review suggests that agents commonly used in AD, including cholinesterase inhibitors and NMDA receptor antagonists, may offer preliminary neurocognitive benefits in ASD, particularly in individuals with lower IQ. Reported improvements span language, executive function, attention and memory, with some indication that younger individuals may derive greater benefit, though robust, large-scale trials are still needed to confirm efficacy and safety [5].

Clinical guidelines recommend first-tier genetic testing, including Chromosomal Microarray Analysis (CMA) to detect Copy-Number Variants (CNVs) and FMR1 CGG repeat expansion testing for Fragile X syndrome. These approaches have demonstrated substantial diagnostic yield, reinforcing the notion that ASD with ID is often associated with rare, highly penetrant genetic variants that influence neurodevelopmental trajectories [5].

The intersection of ASD and AD is further supported by emerging research into shared pathophysiological mechanisms. One prominent hypothesis involves dysfunction in Cerebrospinal Fluid (CSF) clearance pathways, including lymphatic drainage, perivascular (glymphatic) circulation and olfactory/nasal routes. Efficient CSF circulation is critical for the removal of metabolic waste products, including amyloid-β and tau proteins, which are central to AD pathology [4]. Phillips, proposes that impaired CSF drainage may be a unifying mechanism linking ASD and AD, whereby reduced clearance efficiency contributes to neuroinflammation, synaptic dysfunction and eventual neurodegeneration.

These findings support a lifespan model of neurological vulnerability, in which early genetic and neurodevelopmental alterations in ASD may predispose individuals to later neurodegenerative processes. The convergence of genetic susceptibility, altered brain development and impaired metabolic clearance systems provides a compelling framework for understanding the observed epidemiological association between ASD and AD. Importantly, this emerging body of research underscores the need for longitudinal monitoring and early intervention strategies in ASD populations, particularly those with co-occurring ID, to mitigate potential risks associated with cognitive aging (Fig. 1).

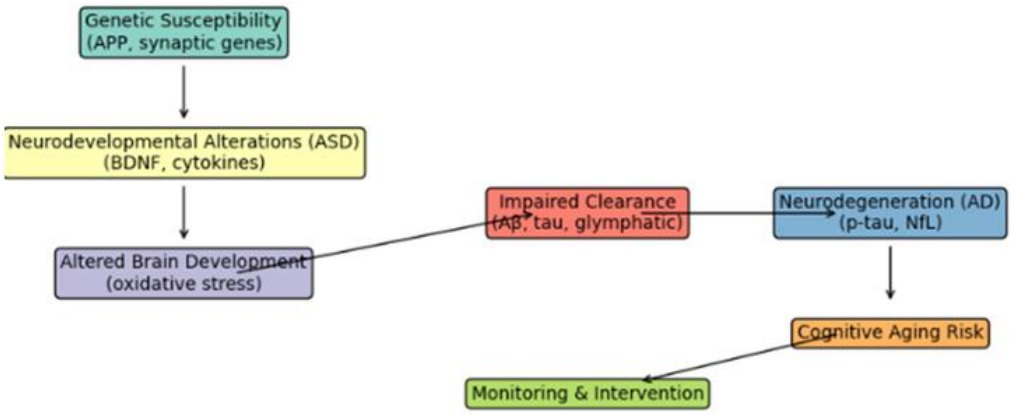

Figure 1: Mechanistic pathway linking neurodevelopmental alterations to neurodegeneration.

The medical evaluation of children with ASD and co-occurring ID often includes first-tier genetic testing, notably chromosomal microarray to detect copy-number variants and targeted FMR1 CGG repeat analysis to screen for Fragile X syndrome [5]. This practice reflects the growing understanding that ASD with ID is genetically heterogeneous, with many cases linked to rare pathogenic variants.

An epidemiological study that examined the prevalence and incidence of dementia among individuals with ASD found that those with ASD and co-occurring ID had a nearly three times increased risk of Alzheimer's Disease (AD) and related dementias in adulthood relative to the general population [5]. Individuals with ASD and co-occurring ID had the highest risk of dementia, even when compared to those without co-occurring ID, in addition to being more likely to be diagnosed with early-onset dementia [5].

The comparison of Autism Spectrum Disorder (ASD) and Alzheimer's Disease (AD) through shared pathophysiologic features offers intriguing insights into the similarities between the two disease states. The authors suggest that diminished Cerebrospinal Fluid (CSF) drainage through the lymphatic, perivascular and nasal turbinates systems may occur in ASD and AD and be an important contributing factor in the development of both disorders [4].

Risk Factors Associated with AS and ASD

The most common genetic risk factor for AD is the APOE-ε4 allele. And, similar to ASD, modifiable risk factors appear to play a substantial role in AD, accounting for 40% of dementia. High Body Mass Index (BMI), high fasting plasma glucose, smoking and obesity are consistently identified as major contributors to the disease burden of AD.

ASD and AD share some genetic risk factors, exhibit overlaps in some pathophysiological mechanisms and experience some of the same environmental exposures. Families that have members with AD are more likely to have children with ASD. Autistic adults under the age of 65 are approximately 2.6 times more likely to be diagnosed with younger-onset dementia compared to the general population.

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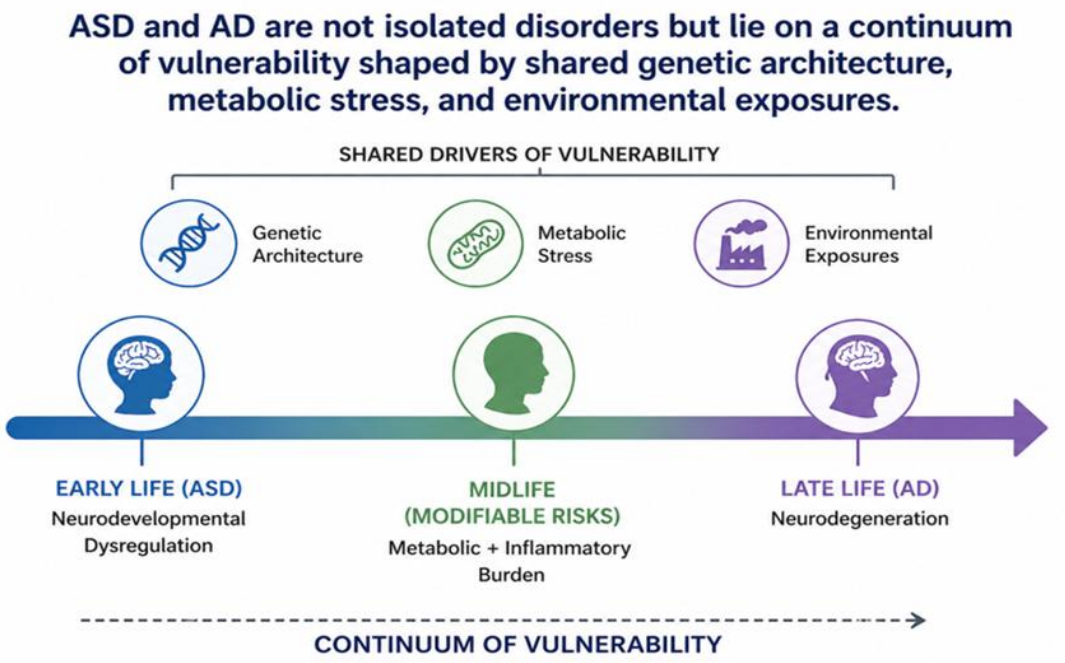

Figure 2: Continuum of vulnerability linking ASD and AD across the lifespan.

The Glymphatic System and Discovery of Meningeal Lymphatics

The authors propose that a contributing factor in disease states such as ASD and AD may be dilated, blood-filled vessels within the nasal turbinates, which can obstruct normal CSF flow through the nasal lymphatics/glymphatic system.

Risk Findings on AD

A growing body of epidemiological and clinical research indicates that modifiable lifestyle factors significantly influence the risk, onset and progression of Alzheimer's Disease (AD).

Smoking

Smoking has been associated with a 70% increased risk of AD and earlier symptom onset, accounting for 14% of global cases. Chronic exposure contributes to neurocognitive decline, including memory deficits, executive dysfunction and global brain atrophy [6].

Poor Sleep Quality

Poor sleep quality shows a bidirectional relationship with AD. Disruptions in sleep, particularly reduced NREM slow-wave activity, are linked to tau pathology and may serve as early biomarkers of cognitive decline [6].

Chronic Stress

Chronic stress and prolonged glucocorticoid exposure are implicated in accelerating AD pathology, likely through hippocampal damage and neuroinflammatory pathways.

Physical Inactivity

Physical inactivity reduces neuroprotective mechanisms such as neurogenesis, synaptogenesis and neurotrophic factor production (e.g., BDNF), thereby increasing vulnerability to cognitive decline [6].

Excessive Alcohol Consumption

Excessive alcohol consumption is associated with neurotoxicity and increased dementia risk, although dose-dependent effects vary across studies [6].

Obesity

Obesity demonstrates a complex relationship with AD: midlife obesity increases risk, while late-life BMI reductions may reflect preclinical disease (reverse causation). Longitudinal data suggests dual mechanisms influencing risk [6].

Poor Diet

Poor diet, particularly high-glycemic and refined carbohydrate intake, promotes amyloid-β accumulation. Malnutrition further worsens outcomes and mortality, with stronger effects observed in APOE-ε4 carriers [6].

Social Isolation

Social isolation has two aspects: objective, which includes the lack of social networks and reduced engagement in social activities and perceived, which encompasses feelings of loneliness and inadequate social support [6]. Evidence suggests a strong correlation between these aspects and cognitive decline [6].

Maternal Metabolic Dysfunction

Maternal metabolic dysfunction, particularly insulin resistance and obesity, has been proposed to influence fetal neurodevelopment. Consistent findings across studies also identify maternal obesity, pregestational diabetes and gestational diabetes as significant risk factors for ASD [4].

Accumulating evidence suggests that metabolic disturbances, including obesity, maternal diabetes and high intake of energy-dense diets, are associated with increased risk of both Autism Spectrum Disorder (ASD) and Alzheimer's Disease (AD).

Recent research implicates glymphatic system dysfunction as a potential shared mechanism in both Autism Spectrum Disorder (ASD) and Alzheimer's Disease (AD). Enlarged perivascular spaces (EPVS), a neuroimaging marker of impaired interstitial fluid clearance, have been associated with cognitive decline, dementia, stroke and cerebral small vessel disease, with hippocampal EPVS specifically linked to AD diagnosis [4].

Advanced imaging studies using Diffusion Tensor Imaging Analysis of the Perivascular Space (DTI-ALPS) reveal that both ASD and AD patients exhibit reduced ALPS indices, suggesting compromised glymphatic clearance function relative to healthy controls (Phillips, 2026). At the molecular level, emerging evidence indicates shared genetic factors between ASD and AD that may influence neurovascular integrity and waste-clearance pathways, further supporting a mechanistic connection via glymphatic dysfunction [4].

Future Directions in Alzheimer's Disease Treatment and Management

Donepezil (Aricept) is the first-line medication for AD. Galantamine (Razadyne), a natural tertiary alkaloid found in plants such as Galanthus nivalis, was identified in the 1950s, along with Tacrine (Cognex) [6]. Digital Therapeutics (DTx) represent a rapidly expanding adjunctive approach. These interventions leverage software platforms (e.g., mobile apps, virtual reality and cognitive training programs) to enhance cognition, memory and functional capacity in AD patients [6]. Evidence suggests DTx may complement traditional care, particularly in early-stage disease and symptom management.

Current evidence indicates that no definitive curative therapy exists for Alzheimer's Disease (AD). While non-pharmacological interventions (e.g., exercise, cognitive training, music and light therapy) provide supportive benefits, their effects on core disease progression remain limited [6].

Immunotherapy is emerging as one of the most promising frontiers in addressing neurodegenerative processes. Among these approaches, novel agents targeting tau pathology, particularly Antisense Oligonucleotides (ASOs), have shown encouraging early results, suggesting the potential to modify disease progression. Other strategies, such as intravenous Immunoglobulin (IVIg) and plasma exchange, have also been explored; however, current evidence indicates that their efficacy is more limited than that of monoclonal Antibody (mAb)-based therapies [6-8].

Conclusion

Emerging evidence highlights convergent features between Autism Spectrum Disorder (ASD) and Alzheimer's Disease (AD), despite their classification as neurodevelopmental and neurodegenerative disorders, respectively. Both conditions exhibit overlapping phenotypes, including cognitive deficits, impaired social behavior and atypical behavioral patterns. Notably, altered neuroimmune signaling has been increasingly implicated in the pathogenesis of both ASD and AD, supporting the hypothesis of a continuum involving immune-mediated neural dysfunction.

Conflict of Interest

The authors declared no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

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Data Availability Statement

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

Ethical Statement

The project did not meet the definition of human subject research under the purview of the IRB according to federal regulations and therefore was exempt.

Informed Consent Statement

Informed consent was obtained from all participants included in the study.

Authors' Contributions

Author approved final version of this paper.

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