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Review

Autism Spectrum Disorder and Intellectual Disability: Where are We Now and What Challenges Lay Ahead?

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Abstract: The coexistence of Intellectual Disability (ID) and Autism Spectrum Disorder (ASD) presents a complex clinical scenario that requires comprehensive and personalized interventions. This article explores the neurobiological mechanisms underlying the comorbidity of ID and ASD, highlighting the shared genetic and synaptic pathways that contribute to both conditions. The discussion also covers the prevalence of comorbidities such as epilepsy, sleep disorders, and gastrointestinal issues, which exacerbate the challenges in diagnosis and treatment. A multidisciplinary approach, combining behavioral, educational, and pharmacological interventions, is essential for addressing the unique needs of individuals with ID and ASD. Future directions point to the use of advanced neuroimaging, artificial intelligence, and personalized therapies based on genetic markers, which promise to revolutionize treatment strategies. Emphasis is placed on the importance of early intervention and lifelong support to improve functional outcomes and quality of life. The need for ongoing research, policy development, and family involvement is underscored as critical factors in optimizing care and inclusion for this population.

Keywords: Intellectual Disability; Autism Spectrum Disorder; Comorbidity; Neurobiology; Personalized Interventions; Early Intervention; Lifelong Support; Biomarkers; Neuroimaging; Artificial Intelligence.

1. Introduction

Autism Spectrum Disorder (ASD) and Intellectual Disability (ID) are neurodevelopmental disorders that have received increasing attention from the scientific community and the general public [1-5]. The prevalence of ASD has increased significantly in recent

decades, with recent estimates suggesting that approximately 1 in 36 children are diagnosed with the condition, reflecting advances in diagnostic criteria and greater awareness of the disorder [6]. According to the DSM-5, ASD is characterized by persistent deficits in social communication and repetitive and restricted behaviours [6-8], while intellectual disability involves significant limitations in intellectual functioning and adaptive behaviour [9].

The etiological factors of ASD and ID are complex and multifactorial, involving an interaction between genetic and environmental components. Recent studies have identified numerous genes associated with ASD and ID, as well as perinatal and environmental risk factors that may contribute to the development of these conditions [10]. In addition to diagnostic and etiological challenges, individuals with ASD and ID often have comorbidities, such as anxiety, depression and epilepsy, which further complicate clinical management and prognosis. Interventions for ASD and ID vary widely, including behavioral, educational and pharmacological approaches, each with their own benefits and limitations [11, 12]. The educational and social inclusion of individuals with ASD and ID remains an important goal, with public policies and support programs playing a crucial role. The impact of these conditions on families and the need for community support are also areas of great importance [13, 14].

This article reviews the current state of knowledge on ASD and ID, highlighting recent advances, persistent challenges and promising areas for future research. We address global and cultural perspectives, emphasizing the need for personalized and inclusive approaches to improve the quality of life of affected individuals and their families.

2. Method

A narrative literature review was conducted using the Medline (PubMed) database from 2012 to 2024, focusing on the comorbidity of Intellectual Disability (ID) and Autism Spectrum Disorder (ASD). A total of 168 articles were initially identified using the MeSH descriptor "(((treatment[title/abstract]) AND (intellectual disability[text word])) AND (autism spectrum disorder[text word])) AND (intellectual disability[title/abstract])". After applying the first set of exclusion criteria—removing titles that did not address the role of personalized, multidisciplinary treatment approaches for ID and ASD comorbidity, studies published outside the 2012–2024 period, and articles not originally published in English—89 articles were retained.

Subsequently, a second set of exclusion criteria was applied by reviewing abstracts, focusing on the relevance of multidisciplinary and personalized interventions in individuals with ID and ASD. This led to the exclusion of 75 additional articles. After this screening, 7 new articles were manually selected based on their relevance to the study topic. To further enrich the discussion and provide a more comprehensive synthesis of qualitative evidence, an additional 32 English-language articles were manually selected and included based on their importance to the field.

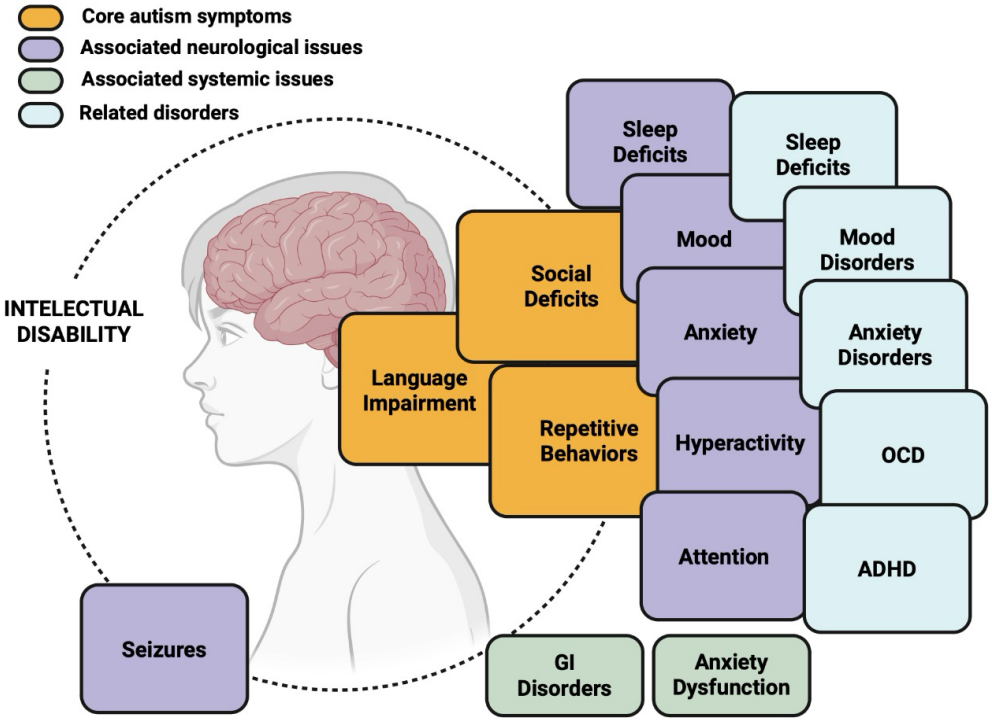
3. Results and Discussion

3.1 Neurobiology of the Relationship Between ID and ASD

The relationship between ASD and ID is complex and involves multiple neurobiological factors [15] (Figure 1). Neurogenetic and neuroanatomical studies indicate that both ASD and ID share pathological pathways that affect brain development, although these conditions may manifest in distinct ways [16]. A deeper understanding of this relationship has been based on advances in molecular genetics, which identify significant overlaps in genetic risk variants associated with both disorders. Genes such as *SHANK3*, *NRXN1*, and *SCN2A*, frequently implicated in ASD, are also involved in intellectual disability phenotypes, suggesting a common basis for synaptic dysfunction, crucial for processes such as neuronal plasticity and learning [17].

From a neuroanatomical perspective, individuals with ASD and ID often exhibit alterations in brain connectivity, particularly in the fronto-parietal network, which is responsible for higher cognitive functions such as planning, attention, and working memory [18]. Additionally, neuroimaging studies have shown that these populations display atypical patterns of cortical growth and organization during the early years of life. Hyperplasia or hypoactivity in regions such as the prefrontal cortex and temporal cortex may contribute to deficits in social and cognitive skills, a central characteristic of both ASD and ID [19].

Figure 1. Overview of Core Symptoms, Neurological and Systemic Comorbidities, and Related Disorders in Autism Spectrum Disorder (ASD).



Synaptic plasticity also plays an important role in the relationship between ASD and ID. Mutations in genes related to proteins that regulate synapses, such as neuroligins and neurexins, directly affect the efficiency and modulation of synaptic transmission, resulting in suboptimal neural circuits that impair cognitive and behavioral development [20]. This synaptic dysfunction contributes to the severity of ID in individuals with ASD, as the integrity of synaptic connections is essential for the development of adaptive cognitive skills.

Another important aspect is the anomalies in the development of the inhibitory GABAergic system, which have been identified in both ASD and ID. These anomalies lead to an imbalance in cortical excitation-inhibition, which is associated with difficulties in sensory modulation, motor control, and cognitive development. The impact of this imbalance is evidenced by stereotyped behaviors and deficits in executive function, common in individuals who present both conditions [21].

Additionally, there is growing evidence about the role of intracellular signaling pathways, such as the mTOR and MAPK pathways, which are involved in critical processes of cellular development, such as neuronal proliferation, migration, and differentiation [22]. Dysfunctions in these pathways have been associated with both ASD and ID, suggesting that impairment in fundamental cellular mechanisms may be a link between

the two conditions. For example, hyperactivity of the mTOR pathway has been associated with excessive dendrite growth and the formation of immature dendritic spines, resulting in dysfunctional neural connectivity, compromising both cognitive and behavioral processing [23].

Finally, the interaction between genetic and environmental factors also plays a crucial role in the overlap between ASD and ID. Prenatal exposures, such as maternal infections and environmental toxins, can act on a vulnerable genome, exacerbating the risk of developing both conditions [24]. In this context, factors such as maternal inflammation and oxidative stress can impact brain development in ways that contribute to the combined phenotypic expression of ASD and ID. Thus, the neurobiology of the relationship between ID and ASD is intricate, involving an interconnected network of genetic, synaptic, circuital, and environmental factors. While understanding this relationship has advanced significantly, much remains to be explored, especially in terms of identifying biomarkers that can predict the cooccurrence of ID in individuals with ASD and developing interventions that can act early on these underlying mechanisms.

3.2 Clinical Aspects of ID with ASD (Prevalence of Comorbidities)

The coexistence of ID and ASD is a phenomenon widely documented in the literature, and the presence of this comorbidity brings significant clinical challenges for both diagnosis and therapeutic management [25]. The prevalence of ID in individuals with ASD ranges from 30% to 50%, depending on the criteria used and the characteristics of the studied population, such as age and symptom severity [26]. This high rate of comorbidity underscores the importance of an integrated and multidisciplinary approach to evaluation and intervention.

Individuals with ID and ASD generally exhibit a broad spectrum of comorbidities, including epilepsy, sleep disorders, gastrointestinal (GI) problems, and psychiatric conditions such as anxiety and mood disorders. Epilepsy is one of the most frequent comorbidities, affecting approximately 20% to 40% of this population [27]. The concomitant presence of ID, ASD, and epilepsy is associated with a worse prognosis, with a higher risk of cognitive and behavioral regression. It is believed that the overlap of these disorders is related to shared abnormalities in neurobiological signaling pathways, such as dysfunctions in synaptic plasticity and regulation of brain rhythms [28].

Another prevalent comorbidity is sleeping disorder, which can manifest as insomnia, sleep apnea, or fragmented sleep. Sleep disturbances affect up to 80% of individuals with ASD and ID, exacerbating behavioral difficulties and impairing learning and memory (Cohen et al., 2014). These sleep problems are often related to dysregulation of the melatonin and circadian systems, as well as difficulties in developing structured sleep routines, especially in individuals with significant communication and emotional regulation deficits.

Gastrointestinal (GI) problems are also frequently observed, with a prevalence that can reach up to 70% of individuals with ASD and ID [29]. These problems include chronic constipation, gastroesophageal reflux, and abdominal pain. The relationship between ASD, ID, and GI problems is not yet fully elucidated, but factors such as intestinal dysbiosis, systemic inflammation, and food hypersensitivity are believed to contribute to the symptomatology. Additionally, the difficulty in expressing physical discomfort, common in individuals with ID and ASD, often results in behavioral crises, complicating clinical management and impairing quality of life.

In terms of psychiatric conditions, anxiety and mood disorders are highly prevalent in individuals with ID and ASD. Anxiety manifests in various forms, including specific phobias, generalized anxiety disorder, and social anxiety. These conditions are often underdiagnosed by individuals with severe cognitive deficits, exacerbating emotional distress and challenging behaviors, such as aggression, self-harm, and resistance to change [30]. Early identification of these comorbidities is critical, as appropriate interventions can mitigate their impact on the individual's overall functionality.

Furthermore, sensory processing disorders are extremely common in the population with ID and ASD. These sensory difficulties manifest hypersensitivity or hyposensitivity to environmental stimuli, generating intense reactions to sounds, lights, textures, and other sensations. Such challenges can lead to repetitive and stereotyped behaviors, which not only interfere with social and cognitive development but also complicate the evaluation and treatment of other comorbidities [31].

In the clinical context, the presence of these comorbidities creates a significant burden for both caregivers and healthcare professionals. The combination of ASD and ID, along with the multiplicity of comorbidities, requires complex care coordination, often involving a multidisciplinary team composed of neurologists, psychiatrists, gastroenterologists, occupational therapists, and other specialists [32]. The lack of specific guidelines for the integrated management of these conditions is a significant gap in clinical practice, reinforcing the need to develop more comprehensive and individualized protocols.

In summary, the clinical aspects of the cooccurrence of ID and ASD are marked by the presence of multiple comorbidities that complicate diagnosis, treatment, and prognosis. The high prevalence of conditions such as epilepsy, sleep disorders, GI problems, and psychiatric disorders highlights the importance of detailed diagnostic approaches and personalized therapeutic interventions. Understanding the interrelationship between these comorbidities is fundamental to improving the quality of life and functional outcomes of this population.

3.3 Treatment and Prognosis of ID with ASD

The treatment of individuals with ID and ASD is multifaceted and must be carefully tailored to the unique needs of each patient, considering both cognitive challenges and behavioral and social difficulties [25]. Due to the overlap of symptoms and the frequent presence of comorbidities, therapeutic approaches involve multidisciplinary interventions that combine educational, behavioral, pharmacological, and psychosocial support strategies.

In the field of behavioral interventions, one of the most used approaches is Applied Behavior Analysis (ABA), which aims to promote adaptive skills and reduce problematic behaviors. ABA is particularly effective in individuals with ASD, but its application to those with comorbid ID requires specific adaptations. Modifications in program intensity and personalization are often necessary, considering the degree of intellectual impairment [33]. For individuals with ID and ASD, structured teaching programs, using positive reinforcement and natural environment teaching, have shown promising results in improving social skills, communication, and independence in daily activities [34.

In addition to behavioral interventions, educational approaches play a central role in managing ID with ASD. Inclusive educational programs that integrate special education techniques and intensive support are essential for maximizing cognitive and functional potential [35]. The integration of evidence-based practices, such as the use of augmentative and alternative communication (AAC) systems, can be particularly useful for nonverbal individuals or those with significant expressive language difficulties. Structured teaching, with the visual organization of routines and tasks, is also widely used, aiming to promote predictability and reduce anxiety, a common problem in individuals with ASD and ID [36].

Regarding pharmacological management, the treatment of psychiatric and behavioral comorbidities, such as anxiety, mood disorders, aggression, and hyperactivity, is often necessary. However, medication selection must be done with caution, considering potential drug interactions and the increased risk of adverse effects in people with severe intellectual disabilities [37]. Atypical antipsychotics, such as risperidone and aripiprazole, have been widely used to manage aggressive behaviors and irritability in individuals with ASD and ID. While effective, these medications require ongoing monitoring due to the risk of metabolic side effects, such as weight gain and endocrine dysfunction [38].

Specific interventions for managing comorbidities, such as epilepsy and sleep disorders, are also critical. In cases of epilepsy, for example, the choice of anticonvulsants must be carefully considered, as some medications may exacerbate behavioral symptoms or interfere with cognition [28]. Additionally, non-pharmacological approaches to improve sleep quality, such as behavioral sleep therapy and the use of melatonin supplements, may be necessary to address sleep disorders, which are highly prevalent and directly impact daytime functionality [39].

From a prognostic perspective, the concomitant presence of ID and ASD is associated with additional challenges in the development of adaptive skills, which negatively impact future independence and quality of life [40]. Longitudinal studies suggest that, in individuals with this dual condition, the progression in the acquisition of motor, social, and communication skills tends to be slower and less consistent compared to individuals with ASD without ID [41]. Furthermore, the severity of intellectual disability is an important predictor of outcome, with those presenting severe ID generally having a more limited prognosis in terms of functional independence and social integration [42].

A critical factor in prognosis is the early initiation of interventions. Robust evidence indicates that the initiation of intensive treatments in early childhood, especially in programs that combine education, behavioral training, and family support, is associated with better cognitive and behavioral outcomes [43]. Family involvement in the therapeutic process is a key element in maintaining the progress achieved and generalizing the skills learned in other contexts, such as the home and community environments [44].

Another relevant aspect of prognosis is the continuous support throughout life. Unlike other developmental conditions, where symptoms may stabilize or significantly improve over time, individuals with ASD and ID often require ongoing support in various areas, including mental health, rehabilitation, and social assistance [45]. This requires the creation of adequate transition programs for adulthood, aimed at preparing individuals to achieve the maximum possible autonomy, with an emphasis on vocational development and independent living skills [46].

In summary, the treatment and prognosis of individuals with ID and ASD demand a personalized and intensive approach, considering the complexity of clinical needs and the potential of everyone. The integration of multidisciplinary interventions, continuous monitoring of comorbidities, and active family involvement are essential components to promote a higher quality of life and maximize functional independence within the limitations imposed by the condition.

3.4 Future Perspectives

The future perspectives for the treatment and management of individuals with comorbid ID and ASD involve a combination of technological advances, new neuroscientific understandings, and changes in clinical and educational approaches. With the growing understanding of the underlying mechanisms of these conditions, there is a trend towards developing more personalized and evidence-based interventions, aiming to maximize individual potential and improve the quality of life for these individuals [35].

In the field of neuroscience, one of the main areas of investigation is centered on identifying biomarkers that can predict the severity of ID in individuals with ASD. The use of advanced neuroimaging techniques, such as functional magnetic resonance imaging (fMRI) and near-infrared spectroscopy (fNIRS), as well as the analysis of brain connectivity patterns, is offering new possibilities for understanding how synaptic development abnormalities and neural connectivity relate to the severity of intellectual deficits [47]. Furthermore, studies on genetics and epigenetics identifying specific molecular pathways and genetic variants associated with comorbidity, which may, in the future, lead to the development of more targeted therapies, including pharmacogenomic interventions [48].

In terms of treatment, future approaches will likely benefit from the personalization of behavioral and educational interventions with the help of digital technologies. The use of artificial intelligence (AI) and machine learning to analyze large volumes of clinical and behavioral data is already beginning to provide insights into how to better tailor treatment plans to everyone's needs [49]. For instance, systems that monitor adaptive skills progress in real-time can dynamically adjust intervention strategies, allowing for more efficient teaching that is adapted to each person's learning pace [50].

Another promising area is the development of digital tools and assistive devices to improve communication and independence for individuals with ID and ASD. Augmented reality (AR) and virtual reality (VR) technologies are being explored as ways to train social and cognitive skills in simulated, controlled environments. These systems can help generalize learning about real-world situations, something that is often challenging for people with these conditions [51]. Additionally, augmentative and alternative communication (AAC) applications are becoming increasingly sophisticated, allowing for greater autonomy for individuals with verbal limitations [52].

On the pharmacological front, the trend is towards finding more targeted treatments with fewer side effects. The development of new drugs that modulate specific pathways involved in cognition and behavior is an area of intense research. Moreover, there is a growing interest in non-pharmacological interventions, such as neuromodulation, which includes techniques like transcranial magnetic stimulation (TMS) and transcranial electrical stimulation (tES). These approaches aim to modulate brain activity precisely, improving specific cognitive and behavioral functions, and have already shown promising results in initial studies [53].

In the field of education and early intervention, future perspectives point to the need for more inclusive and personalized programs that integrate the latest scientific findings. The concept of adaptive education, which uses real-time data to personalize curricula and teaching strategies, is emerging as an approach that can particularly benefit individuals with ASD and ID [54]. The implementation of evidence-based educational practices, such as structured teaching and the promotion of controlled sensory environments will continue to be essential but supported by new technologies that allow for greater precision in intervention adjustments [36].

The transition to adulthood and healthy aging are other topics that will receive greater attention in the coming decades. The creation of lifelong support programs that are not limited to childhood but extend to adult and elderly phases will be crucial to ensuring adequate quality of life and continuous social integration [45]. Community support models, vocational training programs, and the creation of inclusive work environments are areas that demand more investment and innovation, especially for those with ID and ASD, who face additional barriers during the transition to adulthood [46].

Regarding research, the future points to the need for longitudinal studies that follow the development of individuals with ID and ASD throughout their lives. This will not only allow for a better understanding of developmental trajectories but also help identify critical intervention points and predict risk factors that could compromise prognosis [55]. Additionally, there is a growing demand for studies that integrate genetic, neurobiological, clinical, and behavioral data to build more complete models of the interaction between ID and ASD [56].

Finally, it is essential to highlight the importance of public policies and health strategies that promote inclusion and adequate support for this population. The development of specific guidelines for the integrated management of ID and ASD, in both health and educational contexts, will be a priority in the coming years. The creation of interdisciplinary care networks, the strengthening of family support, and the promotion of awareness campaigns are essential measures to ensure that scientific and technological innovations reach all those who need them [44].

In summary, the future of managing ID with ASD will be marked by personalized treatment, technological integration, and advances in the neurobiological understanding

of these conditions. The prospects are promising but require continuous and coordinated efforts among scientists, clinicians, educators, families, and policymakers to ensure that these innovations truly impact people's lives in a meaningful and transformative way.

4. Conclusion

The coexistence of ID and ASD presents significant challenges that require personalized and continuous interventions throughout life, integrating neuroscientific, educational, and technological advances. Although clinical management of these conditions is complex, prospects are promising, with personalized treatments based on biomarkers, assistive technologies, and innovative educational strategies. The success of these approaches depends on a coordinated effort between science, public policy, and family support, aiming to improve the quality of life and promote the inclusion of individuals with ID and ASD at every stage of their journey.

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