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Comorbidities Associated with Autism Spectrum Disorder: Literature Review

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***Abstract*: Comorbidity refers to the presence of two or more coexisting disorders within an individual. This study offers a comprehensive review of the existing literature on comorbidity, focusing on the co-occurrence of psychiatric and medical conditions in individuals with Autism Spectrum Disorder (ASD) across different stages of life—including infancy, childhood, and adulthood. Specific comorbid conditions explored include attention-deficit/hyperactivity disorder (ADHD), epilepsy, gastrointestinal issues, sleep disturbances, feeding difficulties, and toileting challenges.**

***Keywords*: Autism Spectrum Disorder, ASD, Comorbidities, Epilepsy, Sleep problems.**

1. Introduction

Comorbidities refer to the coexistence of one or more additional medical conditions alongside a primary illness in a patient. These associated conditions may be physical or psychological and can influence the diagnosis, management, and overall prognosis [1]. Autism Spectrum Disorder (ASD) is a neurodevelopmental disorder marked by enduring difficulties in social communication and interaction, along with restricted, repetitive patterns of behavior, interests, or activities [2]. These symptoms typically emerge in early childhood. A recent global meta-analysis reported a pooled prevalence of ASD at 1.01% in North America, 0.73% in Europe, and 0.41% in Asia [3]. Individuals with ASD often face a heightened burden of both medical and psychiatric comorbidities. One study found that 74% of individuals with autism had at least one co-occurring condition [4]. Common comorbidities in ASD include attention-deficit/hyperactivity disorder (ADHD), anxiety, mood disorders, sleep disturbances, epilepsy, macrocephaly, migraines or headaches, congenital neurological anomalies, obesity, encopresis, enuresis, and behavioral challenges such as self-injury, wandering, tantrums, food refusal, and aggression [4]-[6]. Additionally, approximately 30% of children with ASD have intellectual disabilities, and another 30% are minimally verbal [6]. Identifying comorbidities in individuals with ASD is crucial for providing comprehensive and effective care. Early recognition of the possible comorbidities enables clinicians to tailor interventions more precisely to the individual's needs. This can lead to improved symptom management, better functional outcomes, and enhanced quality of life.

A. Study Method

This literature review was conducted through a systematic search of multiple electronic databases, including PubMed, Scopus, and Google Scholar, for articles published between January 2000 and April 2024. The search strategy combined keywords and Medical Subject Headings (MeSH) terms such as "Autism Spectrum Disorder," "ASD," "comorbidities," "medical conditions," "psychiatric disorders," and related terms.

1) Inclusion Criteria

- Peer-reviewed articles published in English.
- Studies focusing on comorbid medical and psychiatric conditions in children and adolescents diagnosed with ASD.
- Original research articles, systematic reviews, and meta-analyses.
- Studies reporting prevalence rates, clinical characteristics, or impacts of comorbidities on ASD management.

2) Exclusion Criteria

- Studies exclusively focusing on adult populations with ASD.
- Non-English language publications.
- Case reports, editorials, commentaries, and conference abstracts without full data.
- Articles not primarily addressing comorbidities associated with ASD.

3) Data Extraction and Synthesis

Relevant data were extracted regarding study design, sample size, comorbid conditions assessed, prevalence rates, and clinical implications. Due to heterogeneity in study designs, populations, and outcome measures, a narrative synthesis approach was used to summarize findings.

2. Comorbid medical and Psychiatric Conditions

A. Attention-Deficit/Hyperactivity Disorder (ADHD)

The reported prevalence of AD/HD among individuals with ASD has varied widely, ranging from 14% to 78% [7]. A recent study identified that approximately 18% of children and adolescents diagnosed with ASD also met the criteria for comorbid ADHD [8]. This study further explored factors

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contributing to sleep disturbances in this population and concluded that ADHD was not a significant predictor of sleep-related issues. Additionally, a comprehensive literature review provided insights into the current landscape of neuroimaging studies in ASD [7]. The authors also examined theoretical frameworks and neuropsychological profiles of both disorders, along with potential treatment approaches. Importantly, they highlighted the need to consider social outcomes during treatment planning, noting that children with co-occurring ASD and ADHD face a higher risk of being bullied compared to those diagnosed with either condition alone [7], [9].

B. Epilepsy, Macrocephaly, and Hydrocephalus

Epilepsy is estimated to affect approximately 2–3% of the general pediatric population, whereas the prevalence is notably higher—around 30%—among children with autism [10]. This wide range in reported prevalence is likely due to the heterogeneity of study populations, including differences in age, gender, comorbid conditions, specific subtypes of pervasive developmental disorder (PDD), and the presence of intellectual disability. A retrospective analysis of EEG results and medical records revealed that 40% of referred children were diagnosed with epilepsy [11]. This finding is not unexpected, given that many of the children exhibited epileptic symptoms, with nearly half experiencing seizures. In another study, 10.1% of children and adolescents with ASD were found to have a coexisting epilepsy diagnosis. Interestingly, the study concluded that epilepsy did not significantly contribute to sleep disturbances in individuals with ASD [8]. Seizures are more commonly observed in individuals with ASD when accompanied by intellectual disability or noticeable neurological abnormalities [12]. The risk of seizures increases further in those with additional neurological conditions, such as cerebral palsy [13]. Moreover, language impairment—particularly severe deficits in receptive language—has been identified as a significant risk factor, with the highest seizure rates occurring in children with the most profound language challenges [10].

Macrocephaly is commonly noted in individuals with ASD, especially during the early stages of development. Research indicates that up to 20% of children diagnosed with ASD present with macrocephaly, and in some instances, this is due to rapid head growth occurring within the first year of life. This pattern may reflect atypical brain development, such as increased brain volume or disrupted neural connectivity. Certain genetic factors, including mutations in the PTEN gene, have been linked to macrocephaly in children with ASD and may also play a role in the manifestation of core autism characteristics. Although macrocephaly alone is not sufficient for an autism diagnosis, it may represent a specific neurodevelopmental variant and could prompt further evaluation, including genetic testing and neuroimaging [14], [15].

Studies suggest that individuals with hydrocephalus may have an increased risk of developing neurodevelopmental disorders, including ASD. This association may be attributed to early brain abnormalities, increased intracranial pressure, or disruptions in neural connectivity during critical periods of brain development. Some neuroimaging studies have reported enlarged ventricles or altered CSF dynamics in individuals with ASD, suggesting overlapping neurobiological pathways. Clinically, children with both ASD and hydrocephalus may present with more severe cognitive and behavioral challenges [16].

C. Migraine/Headache

Children with ASD have a higher prevalence of migraine headaches compared to the general pediatric population. Despite this, migraines often go underdiagnosed in children and adolescents with ASD. Research suggests that some forms of ASD may be linked to channelopathies, particularly involving genes such as CACNA1 (calcium voltage-gated channel subunit alpha1), SCN1A and SCN2A (sodium voltage-gated channels), and ATP1A2 [sodium-potassium pump]. Mutations—especially missense variants—in these genes have been implicated not only in ASD but also in various psychiatric and neurological conditions. Notably, the CACNA1A, SCN1A, and ATP1A2 mutations have been associated with familial hemiplegic migraine, indicating a possible shared genetic basis between ASD and migraine [17]-[20].

A study conducted in 2019 reported that individuals with a first-degree relative who experiences migraines have a 1.3-fold increased likelihood of having a child diagnosed with ASD, compared to those without a family history of migraine [21]. Additionally, research has shown that the prevalence of migraine is higher among children with ASD than in the general pediatric population [22].

D. Self-injury, Aggression, Wandering, and Tantrums

Challenging behaviors including self-injury, aggression, wandering, and tantrums are frequently observed in individuals with Autism Spectrum Disorder (ASD), posing significant challenges for caregivers and clinicians. Self-injurious behavior (SIB), such as head banging and biting, affects between 33% and 71% of individuals with ASD and tends to persist over time [23], [24]. Aggressive behaviors occur in approximately half of children with ASD, often directed towards caregivers or peers [25]. Wandering or elopement is a serious safety concern, affecting nearly 50% of children with ASD, which can lead to dangerous situations [26]. Tantrums, characterized by intense emotional outbursts, are more frequent and severe in ASD compared to typically developing children and are often related to communication difficulties and sensory sensitivities [27].

E. Motor Abnormalities

Motor abnormalities are highly prevalent among individuals with Autism Spectrum Disorder (ASD) and are considered one of the early observable signs. A systematic review reported that between 50% and 88% of children with ASD exhibit motor difficulties, including deficits in fine motor control, gross motor coordination, and postural stability [28]. Data from the SPARK study, which analyzed a large cohort of 13,887 children with ASD, found that 88.2% were at risk of motor impairments, with a relative risk 22.2 times higher than in typically developing peers [29]. These impairments often emerge in early childhood

Table 1
Prevalence of comorbidities in children with ASD

Comorbidities	Prevalence rang	Key finding
Gastrointestinal Issues	62% – 81.3%,	Constipation most common; associated with behavior issues
Sleep Disturbances	68% – 80%,	Linked to irritability and reduced functioning
Feeding Problems	62% – 70%,	Often involve selective eating and sensory issues
Epilepsy	10.1% – 30%	Increased risk with intellectual disability or neurological issues

and persist into adolescence and adulthood, contributing to limitations in daily activities and social participation [28], [29]. Despite their significance, motor deficits are not currently part of ASD diagnostic criteria, which may delay recognition and intervention [28]. Early motor assessments and targeted interventions have been shown to improve functional outcomes in children with ASD [29].

F. Gastrointestinal Symptoms

Gastrointestinal [GI] symptoms are among the most common comorbidities in children with Autism Spectrum Disorder (ASD), and they are increasingly recognized for their association with behavioral and developmental challenges. A Saudi retrospective study reported that 81.3% of children with ASD experienced GI symptoms, with constipation being the most common (73.6%), followed by diarrhea and abdominal pain [30]. Another Saudi case-control study confirmed significantly higher rates of GI disturbances in children with ASD compared to typically developing peers, including bloating, undigested food in stool, and mouth ulcers [31]. Internationally, a large systematic review and meta-analysis that included over 15,000 children with ASD found that they are more than four times as likely to experience GI symptoms compared to neurotypical controls, with constipation and abdominal pain being the most frequently reported [32]. These symptoms are not only distressing physically but are also associated with increased irritability, aggression, and sleep disturbances in ASD patients [32]. Despite their prevalence, GI symptoms are often underdiagnosed in autism assessments, highlighting the need for multidisciplinary approaches in management [31], [32].

G. Feeding problems

Feeding problems are highly prevalent among children with Autism Spectrum Disorder (ASD), often presenting as selective eating, food refusal, and difficulties with chewing and swallowing. A recent Saudi cross-sectional study found that 62% of children with ASD experienced feeding difficulties, predominantly selective eating and food texture aversions [33]. Similarly, a study conducted in Egypt reported that children with ASD frequently display food refusal behaviors, delayed feeding milestones, and a limited diet variety, which can contribute to nutritional deficiencies [34]. On a global scale, a systematic review and meta-analysis covering over 4,000 children with ASD revealed that feeding problems affect approximately 70% of this population, with significant impacts on growth, nutritional status, and family stress [35]. These feeding issues are often associated with sensory sensitivities and gastrointestinal comorbidities, emphasizing the need for multidisciplinary intervention strategies [33], [35].

H. Sleep problems

Sleep problems are common in children with Autism Spectrum Disorder (ASD), affecting up to 80% of this population. A Saudi study reported that 68% of children with ASD had sleep disturbances, including difficulty falling asleep, frequent awakenings, and shortened sleep duration [36]. Another Saudi investigation highlighted the association between sleep problems and increased behavioral challenges in ASD children [37]. Internationally, a large cohort study in the United States found a high prevalence of insomnia and circadian rhythm disruptions among children with ASD, correlating with impaired daytime functioning [38]. Additionally, a systematic review from Europe emphasized that sleep disorders in ASD are linked to greater severity of core symptoms and comorbid anxiety and ADHD [39]. These findings stress the importance of early assessment and comprehensive management of sleep problems to improve quality of life in children with ASD [36]-[39].

I. Toileting Problems

Toileting problems, including delayed toilet training, incontinence, and stool withholding, are frequently reported in children with Autism Spectrum Disorder (ASD). A recent Saudi study [2022] found that 38% of children with ASD experienced toileting difficulties, which were strongly linked to sensory processing abnormalities and communication delays [40]. Similarly, a 2021 Egyptian study reported a high prevalence of daytime urinary accidents and constipation-related withholding in children with ASD, highlighting the role of behavioral and sensory challenges [41]. Internationally, a 2020 cohort study in the US showed that toileting issues often persist into school age among children with ASD and are associated with developmental delays and lower adaptive functioning [42]. Furthermore, a 2019 systematic review emphasized the effectiveness of individualized behavioral interventions in improving toileting skills in ASD populations worldwide [43]. These findings underscore the need for early identification and multidisciplinary approaches to manage toileting problems in children with ASD [40]-[43].

J. Intellectual Disability, Language Impairment, and Dyslexia

ASD frequently co-occurs with various neurodevelopmental challenges, including intellectual disability (ID), language impairment, and dyslexia. Intellectual disability is present in approximately 30–40% of individuals with ASD, with a higher prevalence observed in those diagnosed at an earlier age or with more severe core symptoms [44]. Language impairment is another common comorbidity, ranging from mild delays in expressive language to profound deficits in both expressive and receptive communication. Around 25–30% of autistic individuals remain minimally verbal throughout their lives [45].

Table 2
Behavioral and psychiatric comorbidities in children with ASD

Comorbidities	Estimated Prevalence	Clinical notes
ADHD	14% – 78%,	Varies widely; associated with sleep and behavior problems
Anxiety Disorders	40% – 50%	Includes GAD, social anxiety, phobias
Depression,	Up to 40%,	More common in high-functioning ASD
OCD	17% – 37%	Can resemble ASD behaviors; needs careful differential diagnosis

Moreover, dyslexia—a specific learning disorder characterized by difficulties in reading and phonological processing—has been increasingly recognized in autistic populations. Although dyslexia and ASD were once thought to be mutually exclusive, recent evidence suggests a significant overlap, especially in high-functioning individuals with ASD who possess average or above-average intelligence but struggle with reading and decoding written language [46]. These co-occurring conditions can complicate diagnosis and intervention planning, underscoring the importance of comprehensive developmental assessments and individualized educational strategies

K. Psychosis, Depression, and Anxiety Disorders

Individuals with Autism Spectrum Disorder [ASD] are at increased risk for a range of psychiatric comorbidities, including psychosis, depression, and anxiety disorders. Emerging evidence suggests that autistic individuals are significantly more likely to develop psychotic disorders, such as schizophrenia, than the general population, with shared genetic and neurobiological factors potentially contributing to this overlap [47]. Depression is also highly prevalent in individuals with ASD, particularly in those with average or above-average cognitive abilities who may be more aware of their social difficulties and isolation. Studies indicate that up to 40% of autistic individuals may experience clinically significant depressive symptoms during adolescence or adulthood [48]. Anxiety disorders are among the most commonly reported psychiatric comorbidities in ASD, with prevalence estimates ranging from 40% to 50% [49]. These include generalized anxiety disorder, social anxiety, specific phobias, and obsessive-compulsive disorder. The presence of these co-occurring psychiatric conditions can exacerbate core ASD symptoms, impair daily functioning, and reduce quality of life. Therefore, early identification and integrated mental health support are essential components of effective care in this population.

L. Obsessive Compulsive Disorder (OCD)

Obsessive-Compulsive Disorder (OCD) is a frequently reported psychiatric comorbidity in individuals with Autism Spectrum Disorder [ASD]. Both conditions can present with repetitive behaviors and rigid routines, which often leads to diagnostic challenges and misinterpretation of symptoms. While repetitive behaviors in ASD are typically ego-syntonic (perceived as natural or comforting), OCD behaviors are usually ego-dystonic (distressing and intrusive), which helps distinguish the two [50]. Studies estimate that up to 17–37% of individuals with ASD meet criteria for OCD, a significantly higher prevalence compared to the general population [51]. This comorbidity is more commonly observed in adolescents and adults with ASD, particularly those with higher cognitive abilities. Neurobiological studies suggest overlapping dysfunction in cortico-striatal-thalamo-cortical circuits in both disorders, which may explain their clinical similarities [52]. Importantly, when OCD co-occurs with ASD, it may contribute to increased anxiety, greater impairment in daily functioning, and poorer quality of life. Accurate diagnosis and tailored interventions, including cognitive-behavioral therapy [CBT] and pharmacological treatments such as selective serotonin reuptake inhibitors [SSRIs], are crucial in managing OCD symptoms in autistic individuals.

3. Results

The literature reviewed revealed a consistently high prevalence of medical, behavioral, and psychiatric comorbidities among individuals with Autism Spectrum Disorder (ASD). Key findings from both international and regional (especially Saudi and Arab) studies are summarized below:

- *Gastrointestinal (GI) Symptoms*: Prevalence ranged from 62% to 81.3%. Constipation was the most frequently reported symptom, followed by abdominal pain and diarrhea.
- *Sleep Problems*: Found in 68% to 80% of children with ASD. Difficulties included delayed sleep onset, frequent night wakings, and reduced total sleep duration. Sleep disturbances were associated with increased behavioral problems.
- *Feeding Difficulties*: Affecting approximately 62% to 70% of children. Most common issues were selective eating, texture aversions, and food refusal, often linked to sensory sensitivities and GI issues.
- *Epilepsy*: Prevalence ranged from 10.1% to 30%, significantly higher than in the general population. Risk factors included intellectual disability, language impairment, and the presence of neurological anomalies such as cerebral palsy.
- *Motor Abnormalities*: Reported in 50% to 88% of individuals with ASD, including fine and gross motor deficits, postural instability, and coordination issues. A large-scale study (SPARK) found that 88.2% were at risk of motor impairments.
- *Self-Injury, Aggression, and Tantrums*: Self-injurious behavior was observed in 33% to 71% of individuals. Aggressive behaviors affected about 50%, while wandering and elopement were reported in nearly half of cases.
- *Toileting Issues*: Documented in 38% of children with ASD in Saudi studies. These issues were often linked to communication deficits and sensory processing abnormalities.

Table 3
Key finding from Saudi studies on ASD comorbidities

Study Focus	Sample Size	Key Result
Gastrointestinal Symptoms	N=200+,	81.3% had GI issues; constipation most common
Feeding Problems	N=180	62% experienced selective eating and texture aversion
Sleep Problems,	N=150	68% had significant sleep disturbance
Toileting Challenges	N=100	38% with toileting difficulties linked to sensory issues

- *ADHD and Psychiatric Comorbidities*: ADHD co-occurred in 14% to 78% of cases. Anxiety, depression, and OCD were frequently reported and associated with poorer adaptive functioning and increased caregiver stress.

These findings suggest a need for comprehensive, multidisciplinary care models to manage the wide range of comorbidities in children with ASD, with special consideration for early screening and culturally appropriate interventions in Arab populations.

4. Conclusion

A clear understanding of the various comorbid conditions associated with Autism Spectrum Disorder (ASD) is essential for both clinicians and researchers. Considering these co-occurring disorders is crucial for developing and implementing effective intervention strategies tailored to the needs of individuals with ASD. Despite its importance, comorbidity in ASD remains an underexplored area that warrants further research.

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