International Journal of Innovative Technologies in Social Science

e-ISSN: 2544-9435

Scholarly Publisher
RS Global Sp. z O.O.
ISNI: 0000 0004 8495 2390

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ARTICLE TITLE	EXPLORING THE GENETIC AND CLINICAL OVERLAP BETWEEN EHLERS-DANLOS SYNDROME, AUTISM SPECTRUM DISORDER, AND ADHD: A COMPREHENSIVE REVIEW
DOI	https://doi.org/10.31435/ijitss.4(48).2025.4027
RECEIVED	02 October 2025
ACCEPTED	09 December 2025
PUBLISHED	11 December 2025
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EXPLORING THE GENETIC AND CLINICAL OVERLAP BETWEEN EHLERS-DANLOS SYNDROME, AUTISM SPECTRUM DISORDER, AND ADHD: A COMPREHENSIVE REVIEW

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ABSTRACT

Background: Neurodevelopmental disorders, including Autism Spectrum Disorder (ASD) and Attention-Deficit/Hyperactivity Disorder (ADHD), manifest early in life and are characterized by impaired functioning in different life domains. A group of genetic tissue disorders known under the name Ehlers-Danlos Syndrome (EDS) also manifest themselves in early childhood. Recent research points to a possible genetic and symptomatic link between EDS and neurodevelopmental disorders. This review focuses on similar manifestations and co-occurrence of the disorders mentioned above.
Objective: This review investigates the prevalence and significance of comorbid ASD and ADHD in individuals with EDS. Additionally, the genetic and symptomatic connections shared by those conditions are worth exploring, knowing that they could pave the way for joint diagnostic and treatment approaches.
Methods: A systematic literature review was conducted using databases such as PubMed, Cochrane Library, Web of Science, and Google Scholar. Selected studies were chosen based on their focus on the prevalence of ASD and ADHD in EDS patients, genetic or neurobiological links, and statistical analyses of comorbid rates
Results: The prevalence of ADHD in individuals with EDS is significantly higher than in the general population; according to available data, nearly half of EDS patients meet the diagnostic criteria for ADHD. A similar occurrence has been found in individuals diagnosed with EDS - they have a significantly higher chance of being diagnosed with ASD. Shared gene variations between EDS and ASD/ADHD related to synaptic function and neural development have been identified by several genetic studies. The results indicate the possibility of common neurodevelopmental pathways between those conditions. Furthermore, both EDS and ASD/ADHD present with shared symptoms such as joint hypermobility, proprioceptive issues, and autonomic dysfunction.
Conclusion: Numerous reports highlight the higher than-in-population comorbidity rates of ASD and ADHD in EDS patients. This emphasizes the need to implement routine screening and improve the management of individuals suffering from these conditions. Further research into the genetic and neurobiological connections can help introduce new interventions focused on the complexity of the problem and improve results in patient care and quality of life.

KEYWORDS

Ehlers-Danlos Syndrome, Autism Spectrum Disorder, Attention-Deficit/Hyperactivity Disorder, Comorbidity, Genetic Overlap, Neurodevelopmental Disorders

CITATION

Agata Zapałowska, Michał Bielecki, Kamil Kondracki, Anna Bieda, Monika Kondracka, Wojciech Kozłowski, Milena Szczepańska. (2025). Exploring the Genetic and Clinical Overlap Between Ehlers-Danlos Syndrome, Autism Spectrum Disorder, and ADHD: A Comprehensive Review. *International Journal of Innovative Technologies in Social Science*, 4(48). doi: 10.31435/ijitss.4(48).2025.4027

Introduction

Neurodevelopmental disorders are a group of early-onset conditions that impact the formation of the nervous system. There are many shared similarities between them, but impaired functioning is a manifestation that connects them all. These disorders exist on a spectrum, meaning there are varying degrees of impairment among patients. In DSM-5 (American Psychiatric Association, 2013), published in 2013, those conditions were categorized into six different groups:

1. intellectual disability
2. communication disorders
3. autism spectrum disorder
4. ADHD
5. neurodevelopmental motor disorders
6. specific learning disorder

Autism is a neurodevelopmental condition that exists on a spectrum. Most cases are believed to be of idiopathic cause. Research indicates that environmental factors play the most important role in autism pathogenesis. However, growing research focuses on the importance of underlying genetic factors in autism development (Spek, 2014).

Similarly to autism, ADHD is also a part of the broad group of neurodevelopmental conditions. It has been scientifically proven that ADHD is a heritable condition. Genome-wide molecular studies show an increased burden of significant, rare copy-number variants (CNVs) in children with ADHD compared with controls. Recent polygenic risk score analyses have also shown that en masse common variants are enriched in ADHD cases compared with population controls (Martin et al., 2015).

EDS is a group of genetic connective tissue disorders caused by irregular collagen structure, synthesis, or processing. In addition to the conditions mentioned earlier, symptoms of EDS start showing at an early age. The first symptoms might be noticeable as early as in newborn children. Symptoms and severity usually vary depending on the type and might present as mildly loose joins but also lead to severe complications. According to the International EDS Consortium, there are 13 recognized subtypes of Ehlers-Danlos syndrome, of which 12 are considered rare (Malfait et al., 2017). The most common subtype of the condition is the Hypermobile EDS (formerly categorized as type 3). It is believed to be caused by genetic mutations with growing data on possible heritability. However, no genetic test is available to confirm the condition; the diagnosis is solely based on clinical features presented by the patient. (Malfait et al., 2020).

In 2018, in order to understand the genetic basis of EDS, a Hypermobile Ehlers–Danlos Genetic Evaluation (HEDGE) study was launched by the Ehlers-Danlos Society. This study (Ehlers-Danlos Society, 2019) aims to analyze 1021 whole-genome sequences from individuals with hypermobile Ehlers-Danlos syndrome to identify a common genetic marker for the condition. If successfully concluded, this study could change our understanding of EDS and its potential connections with neurodevelopmental disorders. It would lay the foundations for new possible targeted treatments and lead to a tremendous shift in the diagnostic process and management of EDS and its comorbidities.

With our current state of knowledge, we are unable to identify the exact etiology of ADHD, and ASD is known to be primarily an idiopathic cause (National Human Genome Research Institute, 2019). Therefore, it is hard to find scientific evidence connecting hEDS with other neurodevelopmental disorders. (Sieg, 1992).

Despite the underdevelopment of this topic and the limited available data, a few case studies that focus on the co-occurrence of autism and hEDS can be found in medical databases. However, it is undeniable that more research in this area is still necessary. A more thorough investigation could significantly enhance our understanding and management of these conditions, offering better solutions for the future.

Even though this topic is underdeveloped and needs more research, it is worth noticing overlapping symptoms and patterns that indicate a possible connection between those conditions.

Significance of comorbid conditions

Comorbid conditions can complicate the diagnostic process. Symptoms of one condition may conceal or mimic those of another, leading to misdiagnosis or delayed diagnosis (Chatzikonstantinou et al., 2013).

Comprehensive and accurate diagnosis is crucial as it affects the choice of treatment strategies. Misdiagnosis can lead to ineffective or, in some cases, even harmful interventions.

The presence of multiple conditions often exacerbates the severity and incidence of symptoms. For example, chronic pain and fatigue from EDS can worsen attention and focus problems in ADHD or sensory sensitivities in ASD (Battison et al., 2023; Riquelme et al., 2016).

Individuals who present with comorbid conditions experience a more significant impact on daily functioning, employment, and social interactions. This highlights the need to build comprehensive support systems for the patients that could accurately address the unique challenges faced by these individuals. Recognizing and addressing these challenges is critical for improving the quality of life for those affected by these complex conditions.

There are a lot of different overlapping symptoms between h-EDS, ADHD, and ASD. They vary from physical to gastrointestinal and neurological symptoms. Similarities can even be found in genetic variations in the conditions presented.

Sensory issues are a prevalent aspect of Autism Spectrum Disorder (ASD), featuring both hypersensitivity and hyposensitivity. Among intellectually abled individuals with autism, there is a propensity for heightened pain in areas innervated by small, unmyelinated C-fibers (Riquelme et al.,2016). Similar phenomena have been observed in individuals with Ehlers-Danlos Syndrome (EDS) or Hypermobility Spectrum Disorders (HSD), where generalized hyperalgesia and neuropathic pain have been documented. Furthermore, skin biopsies have revealed areas with denervated C-fibers in some cases. A retrospective study, which involved looking back at data from past cases, exploring the co-occurrence of Attention-Deficit/Hyperactivity Disorder (ADHD) and ASD among individuals with either Hypermobile EDS (hEDS)

or HSD demonstrated a higher prevalence of pain and fatigue in those with a dual diagnosis of hEDS+ADHD or hEDS+ASD compared to individuals solely diagnosed with hEDS (Kindgren et al., 2021). This indicates that individuals with such comorbidities may experience exacerbation of symptoms, heightening their sensory experiences.

Twelve years ago, Hakim and Grahame discovered a correlation between hypermobile Ehlers-Danlos syndrome (hEDS) and gastrointestinal (GI) symptoms. Their study revealed that patients with hEDS attending a hypermobility clinic reported a significantly higher occurrence of GI symptoms than age- and sex-matched controls (37% vs. 11%). The most frequently reported GI symptoms were nausea, abdominal pain, constipation, and diarrhea. (McElhanon et al., 2014). The underlying causes of gut symptoms are not fully understood, but they may be linked to connective tissue laxity and its impact on bodily functions (Thwaites et al., 2014). A recent study of a large cohort of young adults with ADHD demonstrated a correlation between ADHD and an elevated prevalence of comorbid functional gastrointestinal disorders (FGID) such as IBS, constipation, and dyspepsia. However, there was no association found between ADHD and somatic immune-mediated GI conditions, such as IBD and celiac disease. The group made up of ADHD patients exhibited a significantly higher frequency of primary care visits for GI symptoms, referrals to GI specialists, and recurrent GI symptoms compared to the control group, indicating a substantial burden of gastrointestinal morbidity in individuals with ADHD and the consequent strain on healthcare resources. (Kedem et al., 2020).

Table 1. Percentage of associated symptoms in 201 children with HSD or hEDS, comparing those with and without a diagnosis of ADHD. (Kindgren et al., 2021)

Symptoms	HSD+hEDS without ADHD	HSD+hEDS with ADHD
Fatigue	50%	88%
Pain	77%	81%
Sleep problems	36%	78%
Gastrointestinal symptoms	57%	66%
Abdominal pain	24%	34%
Constipation	39%	50%
Reflux/Gastritis	14%	28%
Urinary tract problems	10%	28%

Abbreviations: HSD - Hypermobility Spectrum Disorders, hEDS - hyper mobile Ehlers Danlos Syndrome, ADHD - Attention-deficit/hyperactivity disorder

A performed meta-analysis revealed that children with ASD were more than four-fold more likely to develop GI problems than those without ASD and, further, that constipation, diarrhea, and abdominal pain are reported most commonly (McElhanon et al., 2014)

Table 2. Percentage of associated symptoms in 201 children with HSD or hEDS, comparing those with and without a diagnosis of ADHD. (Kindgren et al., 2021)

Symptoms	HSD+hEDS without ASD	HSD+hEDS with ASD
Fatigue	55%	85%
Pain	78%	87%
Sleep problems	42%	92%
Gastrointestinal symptoms	58%	77%
Abdominal pain	26%	23%
Constipation	41%	62%
Reflux/Gastritis	18%	15%
Urinary tract problems	12%	31%

Abbreviations: HSD - Hypermobility Spectrum Disorder, hEDS - hyper mobility Ehlers-Danlos Syndrome, ASD - Autism Spectrum Disorder

Individuals with EDS experience joint hypermobility directly impacting coordination and stability. It can lead to joint dislocation and serious motor complications as a result. (Malfait et al., 2017) Among individuals with autism, impaired motor skills present differently, including impaired movement preparation or planning, gait, and balance. According to the meta-analysis (Fournier et al., 2010), there is a significant difference between individuals with ASD and neurotypical individuals from the control group. It is believed to be linked to atypical neural development and sensory integration issues. According to (Fliers et al., 2008), approximately 1 in 3 children with an ADHD diagnosis presents with motor coordination problems. Data was collected from a CDC-Q questionnaire presented to parents and teachers of children with ADHD. They found that problems with fine and gross motor skills and coordination were related to the inattentive components of the disorder. According to the study, motor coordination problems could be linked to unusual brain development, most likely affecting complex neuronal networks.

Orthostatic intolerance (OI) is frequently observed as a manifestation of intermittent cardiovascular autonomic dysfunction in individuals with hypermobility conditions: it can present as light-headedness or even syncope (Celletti et al., 2017). It is often linked to postural tachycardia syndrome (PoTS). It presents with an elevated heart rate upon standing up, exceeding the established norms for healthy individuals. Orthostatic intolerance has been observed in a large chunk of examined individuals; during autonomic testing, approximately 80% of 35 JHS/EDS-III patients presented with symptoms. Moreover, half of them met the criteria for PoTS. Furthermore, in a conducted survey that consisted of 116 patients diagnosed with JHS/EDS-III, an overwhelming 98% reported experiencing orthostatic intolerance; the symptoms included dizziness after getting out of bed in the morning or after a hot shower (Chan et al., 2019). A study (Owens et al., 2021) using clinical data from 28 patients with a confirmed ASD diagnosis tested autonomic functioning among patients with said diagnosis. The study conducted that among tested individuals, nine presented with PoTS, 4 with PoTS, and vasovagal syncope (VVS). There is a strong indication that the results are associated with undiagnosed hEDS among those individuals.

Genetic research has revealed several common genetic variations linked to both Autism Spectrum Disorder (ASD) and Attention Deficit Hyperactivity Disorder (ADHD). For instance, there are similarities in copy number variations (CNVs) and single nucleotide polymorphisms (SNPs) in genes related to synaptic function and neural development in individuals with these conditions. Specific genes such as CNTNAP2 have been found to be associated with both ASD and ADHD, indicating a shared genetic architecture that impacts neurodevelopmental processes (Dalla Vecchia et al., 2019). Moreover, there is an increasing body of evidence

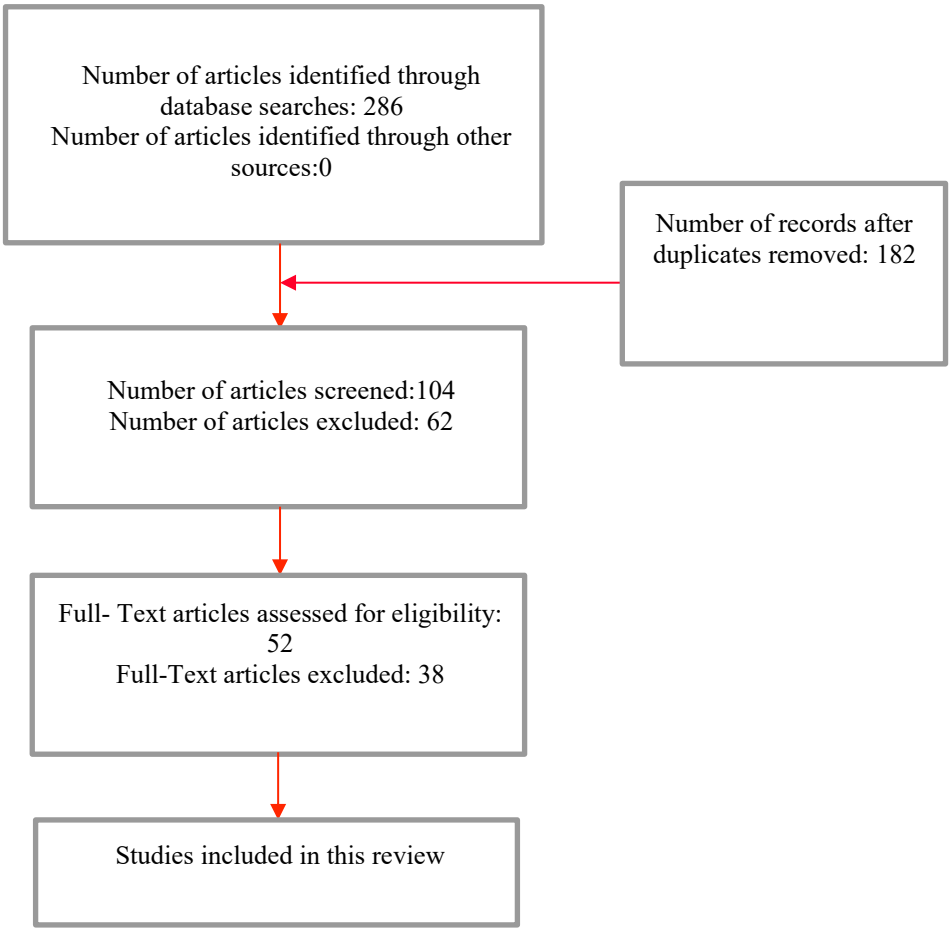
suggesting that genes involved in collagen synthesis and extracellular matrix organization may have an impact on neurodevelopmental pathways, potentially contributing to the co-occurrence of Ehlers-Danlos syndrome (EDS) with ASD and ADHD (Wareham et al., 2024, Bandtlow et al., 2000).

Purpose

This review highlights a possible connection between those conditions. Understanding the prevalence and significance of comorbid ASD, ADHD, and EDS is important; it is essential for developing effective diagnostic criteria, treatment plans, and support systems that may improve the quality of life for affected individuals. This understanding should motivate and guide our commitment to further research and development in this area.

Methods

The primary objective of this review is to summarize the current state of knowledge regarding the prevalence, comorbidity, and shared symptoms between Autism Spectrum Disorder (ASD), Attention-Deficit/Hyperactivity Disorder (ADHD), and Ehlers-Danlos Syndrome (EDS). To gather data for this analysis, we conducted a 7-month long, thorough review of scientific literature, using databases like Pubmed, Cochrane Library, and other peer-reviewed journals, focusing on studies reporting prevalence rates of ASD and ADHD in EDS patients, research discussing the genetic or neurobiological links between these conditions, and articles providing statistical analysis of comorbid rates. We used keywords such as „Ehlers-Danlos Syndrome," „hypermobile EDS," „Autism Spectrum Disorder," „ASD," „Attention-Deficit/Hyperactivity Disorder," „ADHD," „comorbidity," „prevalence," „genetic overlap," "neurodevelopmental disorders“, „shared symptoms“ and combinations thereof. Inclusion Criteria consisted of: studies reporting prevalence rates of ASD and/or ADHD in EDS patients, research discussing the genetic or neurobiological links between these conditions, articles providing statistical analysis of comorbid rates, studies published in English, peer-reviewed journals. Exclusion criteria included: case reports and small case series with less than 10 participants, studies not focused on human subjects, articles without available full texts, non-peer-reviewed sources.



Results

There is a notable comorbidity between Ehlers-Danlos Syndrome (EDS), particularly hypermobile EDS (hEDS), and neurodevelopmental disorders such as Autism Spectrum Disorder (ASD) and Attention-Deficit/Hyperactivity Disorder (ADHD). Multiple studies highlight elevated prevalence rates of these conditions in individuals with EDS compared to the general population. Numerous statistical analyses have supported the elevated comorbid rates of ASD and ADHD in individuals with EDS.

ADHD: A comprehensive study published in the Journal of Attention Disorders analyzed a large cohort of EDS patients and found that nearly half of them met the diagnostic criteria for ADHD. This study highlighted a significantly higher prevalence rate compared to the general population, suggesting a potential underlying genetic or neurodevelopmental link between EDS and ADHD. One study reports 32% of 54 patients with ADHD exhibited generalized hypermobility, compared to 14% in a comparison group (DOĞAN et al., 2011). Furthermore, a comprehensive population-based matched cohort study conducted in Sweden, made up of 1,771 individuals, revealed that those with Ehlers-Danlos syndrome (EDS) were 5.6 times more likely to receive a diagnosis of attention-deficit/hyperactivity disorder (ADHD) when compared to individuals without EDS, with a 95% confidence interval ranging from 4.2 to 7.4.

Thomas et al., 2015	A comprehensive analysis of 175 research studies conducted globally on the prevalence of ADHD in children aged 18 and under revealed an overall combined estimate of 7.2%.
Kindgren et al., 2021	A verified ADHD diagnosis was found in 20% of children with hEDS, while another 7% were under ADHD assessment

ASD: Individuals diagnosed with EDS have a 7.4 times higher likelihood (95% CI: 5.2–10.7) of being autistic compared to a control group (Cederlöf et al., 2016). A study reported that 6.5% of children with HSD or hEDS had a verified diagnosis of autism spectrum disorder (ASD). This prevalence is substantially higher compared to the general child population, where ASD rates are approximately 2.6% (Kindgren et al. 2021).

Zeidan et al., 2022	A 2022 systematic review analyzing global data on autism spectrum disorders (ASD) reported a median prevalence of 1% in children across studies published between 2012 and 2021. The review also identified a pattern of increasing prevalence over time.
Kindgren et al., 2021	In a cohort of children diagnosed with hEDS 7.2%, had a verified diagnosis of autism or Asperger's syndrome in their medical records

While the co-occurrence of ASD, ADHD, and EDS is an emerging area of study, it remains understudied. The evidence suggests that these conditions frequently overlap, but the exact prevalence is yet to be established. This underscores the need for further research, which could provide valuable insights into these complex conditions and their potential interactions.

Discussion

Individuals with hypermobile ehlers-danlos present with higher rates of comorbid ADHD/ASD than the median.

Conclusions

It is worth noting that although autism and EDS/HSD are distinct conditions, they exhibit significant overlap in their characteristics. Genetic data suggests that there are similarities at the molecular, cellular, and tissue levels, as evidenced by several genetic syndromes that are associated with both autism and hypermobility. The co-occurrence of EDS/HSD and autism within families further supports the idea of a potential link between these two conditions.

Authors' Contribution:
Agata Zapałowska - Conceptualization, writing- rough preparation, methodology
Michał Bielecki - Writing- rough preparation, editing, supervision
Kamil Kondracki - review, visualization, investigation
Anna Bieda - Formal analysis, investigation
Monika Kondracka - Writing, proof-reading and editing,
Wojciech Kozłowski - Methodology, supervision, stylistic correctness
Milena Szczepańska - investigation, supervision, methodology
Project administration- Agata Zapałowska

All authors read and approved the final manuscript.

Conflict of interest: The authors declare that there is no conflict of interest.
Funding: This study has not received any external funding.

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