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# Comorbidities in Ehlers-Danlos syndromes and hypermobile spectrum disorders

## *Comorbilidades en los síndromes de Ehlers-Danlos y los trastornos del espectro hipermóvil*

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**ABSTRACT. Introduction:** hypermobile spectrum disorders (HSD) and Ehlers-Danlos syndromes (EDS) are connective tissue disorders often associated with systemic manifestations such as mast cell activation syndrome (MCAS), postural orthostatic tachycardia syndrome (POTS), irritable bowel syndrome (IBS), and autoimmune conditions, including spondyloarthritis (SpA). The overlap of these conditions complicates diagnosis and treatment. This study investigates the prevalence of MCAS and other comorbidities, as well as patterns of medication use, in individuals with HSD/EDS. **Material and methods:** this cross-sectional study included 37 participants diagnosed with HSD or EDS based on the 2017 Diagnostic Consensus Criteria. Participants were divided into two groups: 23 with SpA + EDS and 14 with EDS-only. Demographic variables, comorbidities, and medication use (biologics, disease-modifying antirheumatic drugs [DMARDs], and nonsteroidal anti-inflammatory drugs [NSAIDs]) were analyzed using comparative statistical methods. **Results:** MCAS was significantly less prevalent in SpA + EDS participants (13%) compared to the EDS-only group (85.7%, $p < 0.0001$). POTS (60.9% vs 78.6%) and IBS (60.9% vs 85.7%) occurred at similar frequencies in both groups. The use of immunomodulators was higher in SpA + EDS (73.9%) than EDS-only (42.8%, $p = 0.003$). Biologic use was more common in SpA + EDS (34.8% vs 7.1%, $p = 0.050$), whereas NSAID use was higher in EDS-only participants (47.4% vs 30.4%, $p > 0.05$). **Conclusions:**

**RESUMEN. Introducción:** los trastornos del espectro hipermóvil (TEH) y los síndromes de Ehlers-Danlos (SED) son trastornos del tejido conectivo asociados con manifestaciones sistémicas como el síndrome de activación mastocitaria (SAM), el síndrome de taquicardia ortostática postural (POTS), el síndrome de intestino irritable (SII) y enfermedades autoinmunes como la espondiloartritis (EspA). La superposición de estos trastornos dificulta el diagnóstico y tratamiento. Este estudio analiza la prevalencia de SAM y otras comorbilidades, así como los patrones de uso de medicamentos en pacientes con TEH/SED. **Material y métodos:** se realizó un estudio transversal con 37 participantes diagnosticados con TEH o SED según los Criterios de Consenso Diagnóstico de 2017. Los participantes fueron divididos en dos grupos: 23 con EspA + SED y 14 con SED sin EspA. Se recopilaron datos sobre variables demográficas, comorbilidades y uso de medicamentos, incluyendo biológicos, fármacos antirreumáticos modificadores de la enfermedad (FARME) y antiinflamatorios no esteroides (AINE). Se emplearon métodos estadísticos comparativos para el análisis. **Resultados:** la prevalencia de SAM fue significativamente menor en el grupo EspA + SED (13%) en comparación con el grupo SED sin EspA (85.7%, $p < 0.0001$). La frecuencia de POTS (60.9 vs 78.6%) e SII (60.9 vs 85.7%) fue similar en ambos grupos. El uso de inmunomoduladores fue mayor en el grupo EspA + SED (73.9%) en comparación con el grupo SED sin EspA (42.8%, $p = 0.003$). El uso

**Level of evidence: III (cross-sectional study).**

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the lower MCAS prevalence in SpA + EDS may reflect symptom overlap or suppression due to immunomodulatory treatments. Differences in medication use highlight variations in diagnostic and therapeutic strategies. Comprehensive evaluations are essential to ensure accurate diagnoses and optimal treatment approaches.

**Keywords:** hypermobile spectrum disorders, Ehlers-Danlos syndromes, spondyloarthritis, mast cell activation syndrome, biologics.

de biológicos fue más frecuente en EspA + SED (34.8 vs 7.1%, p = 0.050), mientras que el uso de AINE fue mayor en el grupo SED sin EspA (47.4 vs 30.4%, p > 0.05). **Conclusiones:** la menor prevalencia de SAM en EspA + SED podría deberse a la superposición de síntomas o a la supresión mediada por tratamientos inmunomoduladores. Las diferencias en el uso de medicamentos reflejan variaciones en las estrategias diagnósticas y terapéuticas. Evaluaciones clínicas integrales son esenciales para un diagnóstico preciso y una optimización de los tratamientos en pacientes con TEH/SED y enfermedades autoinmunes asociadas.

**Palabras clave:** trastornos del espectro hipermóvil, síndromes de Ehlers-Danlos, espondiloartritis, síndrome de activación mastocitaria, biológicos.

**Abbreviations:**
AS = ankylosing spondylitis
DMARDs = disease-modifying antirheumatic drugs
EDS = Ehlers-Danlos syndromes
HSD = hypermobile spectrum disorders
IBS = irritable bowel syndrome
MCAS = mast cell activation syndrome
NSAIDs = nonsteroidal anti-inflammatory drugs
POTS = postural orthostatic tachycardia syndrome
SpA = spondyloarthritis

## Introduction

The Ehlers-Danlos syndromes (EDS) and hypermobile spectrum disorders (HSD) represent a range of connective tissue disorders characterized by joint hypermobility, skin hyperelasticity, tissue fragility, and various systemic manifestations. These conditions are inherently complex due to their broad spectrum of clinical signs and symptoms, often leading to delayed diagnoses and numerous comorbidities, such as mast cell activation syndrome (MCAS), postural orthostatic tachycardia syndrome (POTS), irritable bowel syndrome (IBS), and autoimmune disorders frequently observed in affected patients. Additionally, a lack of familiarity among healthcare professionals with the clinical spectrum and diagnostic criteria of EDS and HSD exacerbates these challenges, resulting in misdiagnosis, underdiagnosis, and delayed initiation of appropriate treatment.[1,2,3]

MCAS is characterized by inappropriate mast cell activation, leading to the release of mediators such as histamine, tryptase, prostaglandins, and cytokines. Symptoms of MCAS include flushing, urticaria, gastrointestinal distress, anaphylaxis, and systemic inflammation. Diagnosing MCAS can be challenging due to symptom overlap with other conditions, including POTS and spondyloarthritis (SpA). Current diagnostic criteria emphasize measuring serum tryptase during symptomatic episodes and conducting mediator-specific tests for confirmation. Treatment options include antihistamines, mast cell stabilizers, leukotriene receptor antagonists, and corticosteroids, all tailored to symptom severity and patient response.[4,5,6]

The coexistence of SpA, a group of inflammatory conditions primarily affecting the spine and sacroiliac joints, further complicates the diagnostic process. SpA encompasses inflammatory conditions previously referred to as ankylosing spondylitis (AS) and non-radiographic axial SpA (nr-axSpA). However, recent updates in terminology, as highlighted by van der Heijde, advocate for a shift away from the term ‘ankylosing spondylitis’ to more inclusive nomenclature for axial spondyloarthritis. These conditions present with back pain, sacroiliac inflammation, and systemic features such as uveitis and psoriasis, often associated with the HLA-B27 allele.[3,7,8] Recent advances in imaging, particularly MRI, enable earlier detection of sacroiliac inflammation before structural changes occur and improve diagnostic precision.[8]

The overlap between SpA, MCAS, and HSD/EDS presents diagnostic challenges due to shared symptoms and systemic features. Understanding these relationships is crucial for accurate diagnosis and effective management. Treatments for SpA often involve nonsteroidal anti-inflammatory drugs (NSAIDs), biologics targeting tumor necrosis factor-alpha (TNF-α) or interleukin-17A (IL-17A), and disease-modifying antirheumatic drugs (DMARDs), which address both joint inflammation and systemic manifestations.[8]

This study aims to clarify the interplay between MCAS, SpA, and HSD/EDS by examining comorbidities and treatment patterns, ultimately improving diagnostic precision and therapeutic strategies.

## Material and methods

This study adhered to the ethical principles outlined in the declaration of Helsinki, and the Institutional Review

Board approved it. All participants provided informed consent prior to their inclusion.

A cross-sectional study recruited 37 participants with EDS or HSD diagnosed according to the 2017 Diagnostic Consensus Criteria.[1] Participants were stratified into 23 individuals with co-occurring spondyloarthritis (SpA + EDS) and 14 with HSD/EDS without SpA (EDS-only). Data were collected on demographic variables (age, body mass index), comorbidities (MCAS, POTS, IBS, and upper cervical instability), and medication use (biologics, DMARDs, and NSAIDs).

Descriptive statistics were calculated for continuous variables, including means and standard deviations. Fisher's exact test was used to compare categorical variables, with a significance threshold of $p < 0.05$. Data were analyzed using Microsoft Excel (Microsoft Corporation, Redmond, WA) and SAS software (SAS Institute Inc., Cary, NC).

## Results

MCAS was significantly less common in the SpA + EDS group (13%) compared to the EDS-only group (85.7%, $p < 0.0001$). The prevalence of POTS was similar between the two groups, with 60.9% in the SpA + EDS group and 78.6% in the EDS-only group. Similarly, IBS prevalence was comparable, with 60.9% in the SpA + EDS group and 85.7% in the EDS-only group. Upper cervical instability was reported in 17.5% of participants in the SpA + EDS group and in 21.4% of those in the EDS-only group.

Immunomodulators, including biologics and DMARDs, were significantly higher in participants with SpA + EDS (73.9%) compared to those with EDS-only (42.8%, $p = 0.003$). Biologic use was more prevalent in the SpA + EDS group (34.8 vs 7.1%, $p = 0.050$), while NSAID use was higher in the EDS-only group (47.4 vs 30.4%, $p > 0.05$) *(Table 1)*.

## Discussion

The significantly lower rate of MCAS diagnosis in the SpA + EDS group compared to the EDS-only group may reflect overlapping symptoms and the effects of immunomodulatory therapies. Pain, inflammation, and systemic immune activation (hallmark features of MCAS) are also characteristic of SpA, which may lead to the misattribution of MCAS symptoms. Furthermore, biologics and DMARDs used in SpA may suppress mast cell activity, reducing the clinical expression of MCAS symptoms and complicating diagnosis.[9]

In contrast, similar rates of POTS, IBS, and upper cervical instability across groups highlight the systemic nature of HSD/EDS and the high prevalence of co-occurring conditions. Additionally, some symptoms in the EDS-only group may stem from underdiagnosed rheumatologic conditions rather than MCAS.[3]

Immunomodulatory therapies frequently used in SpA, such as biologics, likely mitigate mast cell activation, reducing the clinical expression of MCAS symptoms and complicating their identification.[5]

In their study of hypermobile EDS, Rodgers et al. found that with comprehensive workups, 67.1% of patients with hypermobile EDS were diagnosed with MCAS.[3] This rate is much closer to the MCAS diagnosis seen in 85.7% of EDS-only participants in this study, suggesting that many of these patients may need additional detailed rheumatological evaluation. The lower rate of MCAS diagnosis in SpA + EDS vs EDS-only supports the hypothesis that many people with HSD/EDS are associated with complicated rheumatological conditions, many of which are either subclinical or undiagnosed and require comprehensive workups.[3,10]

Additionally, recent research has highlighted the strong association between hypermobile Ehlers-Danlos syndrome (hEDS) and neurosurgical comorbidities, particularly craniocervical instability and Chiari I malformation.[11] A retrospective study of 717 individuals with suspected connective tissue disorders revealed that 64% of patients diagnosed with hEDS had a higher prevalence of MCAS and POTS.

B-cell class switching to immunoglobulin E (IgE), a process implicated in mast cell activation, plays a central role in both conditions. In SpA, aberrant B-cell activity has been

**Table 1: Medication use and comorbidities.**

| Variable | SpA + EDS % | EDS-only % | p |
|---|---|---|---|
| Biologic use | 34.8 | 7.1 | 0.05 |
| Immunomodulator use | 73.9 | 42.8 | 0.003 |
| NSAID use | 30.4 | 47.4 | > 0.05 |
| MCAS | 13.0 | 85.7 | < 0.0001 |
| POTS/dysautonomia | 60.9 | 78.6 | > 0.05 |
| IBS/digestive disorders | 60.9 | 85.7 | > 0.05 |
| Upper cervical instability | 17.5 | 21.4 | > 0.05 |

EDS = Ehlers-Danlos syndromes. IBS = irritable bowel syndrome. MCAS = mast cell activation syndrome. NSAID = nonsteroidal anti-inflammatory drugs. POTS = postural orthostatic tachycardia syndrome. SpA = spondyloarthritis.

observed, with class switching to IgE facilitating mast cell activation via high-affinity FcεRI receptors.[12,13] Activated mast cells release proinflammatory mediators, contributing to localized and systemic inflammation. Additionally, the presence of IL-17A-positive mast cells at enthesis sites underscores their integral role in the inflammatory cascade of SpA. These overlapping mechanisms blur the diagnostic distinction between MCAS and SpA and suggest that MCAS-like symptoms may often be subsumed under the broader inflammatory processes associated with SpA.[13]

The distinct medication use patterns observed between groups highlight differences in disease management strategies. Immunomodulator use was significantly higher in the SpA + EDS group (73.9%) compared to the EDS-only group (42.8%), with biologic use at 34.8% versus 7.1%, respectively. These findings are consistent with the inflammatory and autoimmune burden in SpA + EDS, necessitating targeted therapies. In contrast, NSAID use was more common in the EDS-only group (47.4%), reflecting a more symptomatic approach to pain management and may suggest undertreatment as more comprehensive autoimmune workups have not been pursued.[10]

This study's single-center design and the inherent variability in HSD/EDS presentation may limit the generalizability of these findings. Further investigation is warranted into the interplay between B-cell-mediated IgE production, mast cell activation, and the shared inflammatory pathways in MCAS and autoimmune conditions. These studies could clarify the relationships between these conditions and inform strategies to refine diagnostic and therapeutic approaches.

## Conclusions

This study highlights the complex interplay between MCAS, systemic inflammation, and autoimmune conditions in HSD/EDS patients. The lower rate of MCAS diagnosis in the SpA + EDS group illustrates the challenges posed by overlapping symptoms and immunomodulatory treatments. Recognizing co-occurring autoimmune conditions and adopting multidisciplinary approaches are essential for improving diagnosis and management. Further research into shared mechanisms and targeted therapies will enhance care for this complex patient cohort.

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