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A Narrative Review of Hypermobile Ehlers-Danlos Syndrome: Diagnostic Challenges and Opportunities in Primary Care

Revisión narrativa sobre el síndrome de Ehlers-Danlos hipermóvil: desafíos y oportunidades diagnósticas en atención primaria

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Abstract:

Hypermobile Ehlers-Danlos syndrome (hEDS), an autosomal dominant condition, is the most common subtype of hereditary connective tissue disorders. It presents a significant challenge in primary care due to its variable phenotype, multisystemic involvement, and the absence of a known genetic marker. This narrative review aims to summarize the existing evidence for its clinical recognition, promote a multidisciplinary approach, and highlight its relevance in primary care to improve comprehensive management. Based on the diagnostic criteria established by an international consortium in 2017 and considering the lack of a specific management guideline, a review of the updated information on the clinical manifestations of hEDS was conducted. This analysis focused on identifying aspects that could facilitate early detection at the primary care level, including differential diagnoses and the diverse multisystemic presentations of of hEDS across the lifespan. The role of the primary care physician in identifying these cases, as well as their multidisciplinary management and referral according to clinical manifestations, is emphasized. Early recognition of hEDS can curtail years of medical referrals and significantly improve patients' quality of life.

Keywords:

Hypermobile Ehlers-Danlos syndrome, joint hypermobility, clinical diagnosis, autosomal dominant, primary care, connective tissue disorders, rare diseases, family medicine.

Resumen:

El síndrome de Ehlers-Danlos hipermóvil (hEDS), una condición autosómica dominante, es el subtipo más frecuente de los trastornos hereditarios del tejido conectivo. Representa un desafío diagnóstico en el primer nivel de atención por su fenotipo variable, afectaciones multisistémicas y por carecer de un gen asociado. Esta revisión narrativa tiene como objetivo mostrar la evidencia existente para su reconocimiento clínico, promover un enfoque multidisciplinario y destacar su relevancia en el primer nivel de atención médica para mejorar su manejo integral. Con base en los criterios diagnósticos establecidos por un consorcio internacional en 2017, y considerando la ausencia de una guía de manejo específica, se llevó a cabo una revisión de la información actualizada sobre las manifestaciones clínicas del hEDS. Este análisis se centró en identificar los aspectos que podrían facilitar la detección precoz en el primer nivel de atención, incluyendo los diagnósticos diferenciales y las diversas expresiones multisistémicas del hEDS a lo largo de la vida. Se enfatiza el papel del médico de primer nivel en la identificación de estos casos, así como su manejo multidisciplinario y derivación acorde con las manifestaciones clínicas. El reconocimiento temprano del hEDS puede reducir años de interconsultas médicas y mejorar significativamente la calidad de vida de los pacientes.

***Palabras Clave**:*

Síndrome de Ehlers-Danlos hipermóvil, hipermovilidad articular, diagnóstico clínico, autosómica dominante, atención primaria, enfermedades del tejido conectivo, enfermedades raras, medicina familiar

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INTRODUCTION

The Ehlers-Danlos syndromes (EDS) comprise a clinically and genetically heterogeneous group of hereditary connective tissue disorders defined by generalized joint hypermobility, skin hyperextensibility, tissue fragility, and a broad spectrum of systemic manifestations.[1] In 2017, the International Consortium on Ehlers-Danlos Syndromes established a new classification recognizing 13 EDS subtypes based on clinical, molecular, and genetic criteria.[1,2] Among these, the hypermobile subtype (hEDS)—listed in the Online Mendelian Inheritance in Man database (OMIM 130020) and in the international reference portal for rare diseases and orphan drugs (Orphanet; ORPHA code 285)—is the most prevalent. Nevertheless, diagnosing hEDS remains a significant diagnostic challenge, particularly in primary care settings, where its features may be confounded with more prevalent musculoskeletal conditions or functional disorders. This difficulty is compounded by the absence of a confirmatory genetic test[2,3], rendering identification entirely dependent on clinical criteria. In this context, the primary care physician plays a pivotal role in facilitating timely diagnosis and coordinating multidisciplinary management. The absence of a confirmatory genetic test, coupled with limited clinical familiarity regarding the syndrome's phenotypic further exacerbates diagnostic delays.[4,5] Consequently, patients often endure a prolonged diagnostic odyssey, consulting multiple specialties and receiving misdiagnoses or symptomatic treatments that fail to address the underlying systemic etiology[5,6]

This narrative review synthesizes current evidence regarding hEDS aiming to provide primary-care physicians with a practical clinical tool and a comprehensive perspective of the disorder. It addresses its clinical manifestations, updated diagnostic criteria, and relevant differential diagnoses through a system-based approach grounded in the latest scientific evidence. Furthermore, it underscores the importance of recognizing this multisystemic and frequently underdiagnosed condition, promoting coordinated, evidence-based, and person-centered care. By fostering and empathetic approach, this review seeks to address the actual needs of patients from the initial clinical encounter.

PREVALENCE

The prevalence of hEDS remains poorly defined. Population-based studies applying the 2017 diagnostic criteria are limited, complicating an accurate estimation of its frequency. According to ORPHANET (ORPHA:285), prevalence is estimated to range between 1 in 5,000 and 1 in 20,000 exhibiting a notable female predominance. To date, no population-based studies in Mexico have documented the prevalence of hEDS. However, recent research in the United Kingdom has estimated higher rates, such as 1 in 3,100[7], suggesting that hEDS may be significantly underdiagnosed. This underestimation is linked to the syndrome's broad phenotypic variability and the nonspecific nature of its clinical manifestations, which frequently overlap with various etiologies. In non-specialized settings, this obscures recognition and predisposes to more common alternative diagnoses. Additionally, the presence of chronic musculoskeletal pain and psychiatric symptoms −such as anxiety or somatization− may overshadow the underlying condition, directing clinical attention toward more frequent prevalent disorders and contributing to the under-recognition of hEDS in general medical practice.

PHENOTYPE

The clinical presentation of hEDS characterized by generalized joint hypermobility (GJH), chronic musculoskeletal pain, joint instability, and persistent fatigue.[2,4,8] Additionally, dysautonomia-related symptoms −including syncope, orthostatic intolerance, and postural orthostatic tachycardia syndrome (POTS)− are frequently associated with the condition.[9] Functional gastrointestinal disorders are also highly prevalent, including dyspepsia, constipation, and early satiety.[10] In the neuropsychiatric domain, comorbidities such as generalized anxiety, depression, and sleep disturbances have been documented, reflecting the systemic and psychosocial impact of the syndrome.[11] This multisystemic presentation often leads to to diagnostic fragmentation and underscores the necessity of a comprehensive evaluation, this is particularly vital at the primary care level, where clinicians can synthesize these findings to streamline both the diagnostic process and therapeutic approach.[2,12]

INITIAL EVALUATION AND DIAGNOSIS

Given the clinical complexity of hEDS, the role of the primary care physician is essential. Applying the 2017[1] clinical diagnostic criteria, alongside the systematic use of the Beighton score to assess joint hypermobility[3,13,14], empowers primary care providers to effectively identify suspected cases. A system-based clinical examination that accounts for phenotypic variability facilitates the identification of patterns consistent with hEDS. Maintaining a high index of clinical suspicion, excluding alternative pathologies, and ensuring timely referral to specialties −such as medical genetics and rheumatology− are pivotal steps toward establishing a definitive diagnosis. Furthermore, multidisciplinary coordination involving dermatology, psychiatry, nutrition, physical medicine and rehabilitation, cardiology, and neurology− tailored to each patient's specific needs promotes a comprehensive and person-centered approach.

DIAGNOSTIC CRITERIA FOR hEDS

The 2017 international consensus updated the classification of Ehlers-Danlos syndrome subtypes, establishing that the hypermobile type (hEDS) is diagnosed exclusively through clinical evaluation and the exclusion of alternative conditions.

Unlike other subtypes that rely on molecular confirmation, hEDS remains a clinical diagnosis.[1] Recent data from The Ehlers-Danlos Society, indicate that over 99 % of study participants fulfilled the current clinical criteria while fewer than 1% harbored genetic variants suggestive of other connective tissue disorders, further validating the rigor of these guidelines.[15]

Table 1. *Diagnostic criteria for hEDS.*[1,16]

Criterion	Description	Condition to Fulfill
1. Generalized Joint Hypermobility (GJH)	Assessed using the Beighton score, adjusted for age and sex.	Score ≥5 in adults <50 years; ≥4 in adults ≥50 years. Historical evidence (5-point questionnaire) may be considered if the score is one point below the cutoff
2. Clinical manifestations consistent with hEDS	Presence of systemic signs, positive family history, or musculoskeletal complications.	At least 2 of the following 3 features must be met:
A. Systemic signs of a connective tissue disorder	Soft skin, atrophic stretch marks, flat feet, hernias, dysautonomia, fatigue, gastrointestinal disorders, slow wound healing, proprioceptive alterations.	At least 5 positive signs required.
B. Recurrent musculoskeletal manifestations	Chronic pain, frequent dislocations or subluxations.	At least one must be present.
C. Family history of hEDS	Confirmed diagnosis in a first-degree relative.	Documented clinical evidence.
3. Exclusion of other conditions	Other EDS subtypes, hereditary connective tissue disorders, and syndromes with secondary hypermobility must be ruled out.	Clinical and genetic evaluation as available.

* Clinical evaluation should consider the patient's age, sex, and individual context.

To confirm the diagnosis, three criteria must be met:

1. Generalized Joint Hypermobility (GJH).
2. Clinical manifestations consistent with hEDS (requiring at least two of the following: Features A, B, or C).
3. Exclusion of alternative connective tissue disorders.

Within the feature A, at least five systemic signs are expected for the component to be considered positive (see Table 1).[1,16] This diagnostic structure highlights the need for a comprehensive clinical evaluation from the initial medical encounter.

DIFFERENTIAL DIAGNOSES

Due to the lack of a definitive molecular marker, the diagnosis of hEDS relies on the systematic exclusion of conditions with overlapping phenotypes.[1] The most relevant differential diagnoses are summarized in Table 2.[12,16–18]

Table 2*. Descriptive elements to perform differential diagnoses with hEDS.*[12,16-18]

Condition	OMIM ORPHA	Gene(s) Involved	Key Clinical Features	Main Clinical Risks
cEDS	130000 287	*COL5A1*, *COL5A2*	Skin hyperextensibility, atrophic scars, frequent bruising	Skin fragility, surgical complications
vEDS	130050 286	*COL3A1*	Characteristic facial features, translucent skin, spontaneous rupture of vessels, uterus, and intestines	Spontaneous arterial, visceral, and uterine rupture
kEDS	225400 1900	*PLOD1*, *FKBP14*	Congenital hypotonia, early-onset scoliosis, severe myopia	Progressive scoliosis, motor disability
Marfan Syndrome	154700 558	*FBN1*	Tall stature, marfanoid habitus, ectopia lentis, aortic dilation	Aortic aneurysm, aortic dissection
Loeys-Dietz Syndrome	609192 60030	*TGFBR1*, *TGFBR2*	Hypertelorism, bifid uvula, early aneurysms, fragile skin	Cerebral, aortic, and visceral aneurysms
Osteogenesis Imperfecta	166200 216796	*COL1A1*, *COL1A2*	Multiple fractures, blue sclerae, dentinogenesis imperfecta	Recurrent fractures, bone deformities
hEDS	130020 285	Not identified	Joint hypermobility, chronic pain, dysautonomia, gastrointestinal and psychiatric symptom	Functional disability, chronic pain, psychosocial impact

*Abbreviations: EDS: Ehlers-Danlos Syndrome. cEDS: Classical EDS. vEDS: Vascular EDS. kEDS: Kyphoscoliotic EDS. hEDS: Hypermobile EDS.

This table outlines the differential diagnosis between hEDS and other hereditary connective tissue disorders. OMIM (https://www.omim.org/) and ORPHANET (https://www.orpha.net/es/disease) identifiers are included to expedite consultation in specialized databases, alongside associated genes, hallmark clinical features, and primary clinical risks. This comparative framework assists in clinical decision-making and ensures timely referral to medical genetics when overlapping phenotypes are encountered.

hEDS exhibits significant phenotypic overlap with other hereditary connective tissue disorders, including Marfan syndrome, Loeys-Dietz syndrome, and other EDS subtypes−notably the classical (cEDS) and vascular (vEDS) forms.[16–18]

These conditions may share clinical features such as joint hypermobility, valvular prolapse, dysautonomia, skeletal deformities, and tissue fragility. However, they diverge significantly in prognosis and the risk of life-threatening complications, such as aortic aneurysms or spontaneous visceral rupture.[16,18] Effective diagnostic differentiation requires a methodical assessment of multisystemic findings, a detailed family history, and the rigorous application of the 2017 international classification. In this context, tools such as the Beighton score, the Five-Point Questionnaire (5PQ), and targeted examination of cutaneous, cardiovascular, and skeletal signs are paramount for guiding the differential diagnosis and ensuring clinical accuracy.[19,20]

The Beighton score is a standardized instrument for assessing joint hypermobility, comprising nine points across five bilateral and midline maneuvers. Interpretation must be age- and sex-adjusted, as joint laxity naturally diminishes over time. For adults under 50, a score ≥5 indicates generalized joint hypermobility (GJH); for those aged 50 and older, the diagnostic cutoff is reduced to ≥4. When the score falls one point below the threshold, historical evidence −often captured through the Five-Point Questionnaire− may be considered, including a background in activities requiring extreme flexibility such as ballet, gymnastics, or yoga.[13,20,21]

The Five-Point Questionnaire (5PQ) is a useful screening tool for identifying joint hypermobility in adults, especially when the Beighton score cannot be directly applied. It assesses the personal history of extreme flexibility, joint dislocations, and the ability to perform highly mobile postures, as well as family history. A positive result (≥2 affirmative answers) suggests generalized joint hypermobility and may support the diagnostic suspicion of hEDS.[19]

These tools aid in differentiating hEDS from other hereditary connective tissue disorders that present with overlapping manifestations, such as joint hypermobility, chronic musculoskeletal pain, and cardiovascular abnormalities.

CLINICAL PHENOTYPE BY SYSTEMS

hEDS exhibits a highly heterogeneous clinical phenotype, with multisystemic manifestations that evolve over the lifespan, posing a significant diagnostic challenge. The following section provides an overview of the predominant clinical features, organized by system (Table 3).

Musculoskeletal System

Musculoskeletal manifestations constitute the clinical cornerstone of hEDS and are a primary driver for medical consultation. Chronic pain, typically nociplastic in nature, is often diffuse, migratory, and persistent, with exacerbations triggered by physical exertion or joint instability. The latter, secondary to generalized ligamentous laxity, predisposes to recurrent dislocations and subluxations, particularly involving the shoulders, knees, and ankles.

Table 3. *Clinical Manifestations of hEDS by System.*[4,5,9-11,21-29]

System	Clinical Manifestations	Collaborating Specialties
Musculo-skeletal	- Chronic nociplastic pain (diffuse/migratory) - Recurrent dislocations and subluxations (shoulders, TMJ, digits) - Pes planus, hyperlordosis, mild scoliosis - Joint hyperlaxity - Muscle weakness and fatigue - Fine motor delay - Proprioceptive deficits - fine motor delay	PM&R (Physiatry), Rheumatology, Physical Therapy, psychology/psychiatry.
Skin and Connective Tissue	- Velvet-like (silky) skin - Mild to moderate hyperextensibility - Thin, translucent skin (visible venous pattern) - Atrophic striae (unrelated to weight changes) - Skin fragility and easy bruising - Abnormal scarring - Raynaud's phenomenon and chilblains	Dermatology
Cardio-vascular	- Palpitations - Orthostatic intolerance - Vasovagal syncope - Exertional Dyspnea - Mitral valve prolapse - Mild aortic dilation	Cardiology
Autonomic (Dysauto nomia)	- Postural Orthostatic Tachycardia Syndrome (POTS) - Neurocardiogenic syncope - Orthostatic hypotension - Thermal and exercise intolerance - Hyperhidrosis - Chronic fatigue	Neurology, Autonomic Specialists.
Gastro-intestinal	- Gastroesophageal reflux GERD - Chronic constipation - Functional dyspepsia - Early satiety - Food intolerance - Possible gastroparesis and intestinal dysmotility	Gastro-Enterology, Nutrition
Psychiatric and Neuro cognitive	- Generalized anxiety - Reactive depression - Sleep disturbances - Somatization - Hypervigilance (Heightened bodily awareness) - Psychosocial impact of diagnostic delay	Psychiatry, Psychology

*Clinical manifestations of hEDS are categorized by

physiological systems. Key musculoskeletal, cutaneous, cardiovascular, autonomic, gastrointestinal, and neurocognitive findings are outlined, highlighting both their diagnostic significance and their cumulative impact on functional capacity and quality of life.Furthermore, a high prevalence of proprioceptive deficits, muscle weakness, and fatigue has been documented, all of which contribute to progressive functional decline.[4,6,21,22] In this context, the clinician is pivotal in the early recognition of chronic pain as a cardinal manifestation of hEDS. A biopsychosocial approach facilitates managing not only the sensory components of pain but also its profound emotional and social implications. Through longitudinal follow-up, the physician can coordinate multimodal, non-pharmacological interventions −such as tailored physical therapy, self-management education, and psychological support− thereby mitigating excessive medicalization and fostering patient-centered care strategies.

Skin and Connective Tissue

Cutaneous manifestations for hEDS reflect structural defects within the extracellular matrix. Although typically less pronounced than in other EDS subtypes, their presence provides critical diagnostic guidance when observed alongside musculoskeletal and systemic findings. Distinguishing features include a soft or velvet-like skin texture, mild-to-moderate skin fragility, and atrophic scarring.[23]

Dermatologic management must account for tissue friability, prioritizing the avoidance of unnecessary invasive procedures, adopting steroid-sparing approaches, and promoting rigorous skin care. These cutaneous alterations may stem from both extracellular matrix dysfunction and mast cell-mediated inflammatory processes pathways, which potentially underlie symptoms such as urticaria, pruritus, and recurrent episodic flushing.[24]

Cardiovascular System

Cardiovascular manifestations in hEDS, while generally not life-threatening, can impose a substantial symptomatic burden. Common clinical findings include orthostatic hypotension, palpitations, vasovagal syncope, and dyspnea, frequently occurring within the broader framework of dysautonomia. A survey-based study involving patients with hEDS and hypermobility spectrum disorders (HSD) revealed that over 80% reported symptoms consistent with orthostatic intolerance, underscoring the need for routine clinical screening in general practice. Although mild aortic root dilation and mitral valve prolapse may occur, their prevalence is notably lower than in other EDS subtypes and their course is usually benign.[23]

Autonomic System (Dysautonomia)

Autonomic dysfunction is a frequent and debilitating manifestation in hEDS, exerting a significant impact on quality of life. Common syndromes include Postural Orthostatic Tachycardia Syndrome (POTS), neurocardiogenic syncope, and orthostatic hypotension, often accompanied by palpitations, thermal and exercise intolerance, hyperhidrosis, and chronic fatigue. A clinical triad comprising dysautonomia, hypermobility spectrum disorders (HSD), and Mast Cell Activation Syndrome (MCAS) suggests a complex pathophysiological interaction between autonomic regulation, the extracellular matrix, and neurogenic inflammation.[9,24,25] These symptoms are frequently misinterpreted or dismissed as purely functional or psychogenic in origin.

Gastrointestinal System

Gastrointestinal manifestations in hEDS are frequent and multifactorial. Functional symptoms predominate, including dyspepsia, early satiety, chronic constipation, and gastroesophageal reflux, all of which are linked to intestinal motility disorders, visceral hypotonia, and dysautonomia. These patients are frequently diagnosed with irritable bowel syndrome. Research indicates that gastrointestinal dysfunction −specifically gastroparesis and poor tolerance to enteral feeding may reflect a systemic involvement of the gut-brain axis, particularly within the context of chronic or critical illness. Although the study focuses on hospitalized patients, its findings regarding the relationship between dysmotility, inflammation, and feeding tolerance are applicable to hEDS population.[10,25,26] This reinforces the necessity for functional assessments and individualized nutritional support.

Psychiatric and Neurocognitive Manifestations

Neuropsychiatric alterations in hEDS include generalized anxiety, depression, sleep disturbances, and heightened bodily awareness. These manifestations are closely associated with chronic pain, dysautonomia, and diagnostic delay, all of which significantly impair quality of life. An increased perception of physical discomfort, coupled with medical frustration, contributes to the patient's emotional burden. Individuals with multisystemic conditions such as hEDS exhibit greater vulnerability to mood disorders, reinforcing the necessity for a comprehensive multidisciplinary evaluation.[5,11,27–29]

Natural History

hEDS exhibits a multisystemic clinical progression that evolves throughout the life cycle. Although the clinical course is not uniform across all patients, a generalized chronology has been established. This framework facilitates the visualization of the syndrome's clinical trajectory and informs the planning of preventive, diagnostic, and therapeutic interventions starting from the primary care level (Table 4).

During childhood and adolescence, motor and musculoskeletal signs predominate, including joint hypermobility, frequent falls,

fatigue, and nonspecific pain. These symptoms are often overlooked or dismissed as developmental variants, resulting in fragmented clinical approaches that fail to incorporate a comprehensive syndromic perspective.[8,30,32]

In youth and early adulthood, the cardinal manifestations of hEDS become increasingly consolidated, encompassing chronic pain, dysautonomia, functional gastrointestinal symptoms, and neuropsychiatric alterations. This stage frequently coincides with an escalation in both functional and emotional burden, necessitating a biopsychosocial approach that incorporates longitudinal support and interdisciplinary coordination.[31]

Table 4: *Natural evolution of hEDS by life stages.*[8,30-32]

Life Stage	Predominant Clinical Manifestations	Biopsychosocial Effects
Childhood and Adolescence (0-20 years)	- Mild psychomotor delay - Hypotonia, motor incoordination - Joint pain ("growing pains") - Dislocations/subluxations - Early striae - Headaches - Functional constipation - Easy fatigability	Academic, athletic, and social difficulties.
Youth and Early Adulthood (20-40 years)	- Chronic musculoskeletal pain - Persistent fatigue - Dysautonomia (POTS, syncope) - Functional gastrointestinal disorders - Anxiety, depression - Joint instability - Pelvic/bladder dysfunction	Medical frustration and somatization. Anxiety and depression. Impact on education and employment.
Middle and Late Adulthood (40 + years)	- Progressive joint stiffness - Generalized pain - Increased fall risk - Mitral valve prolapse; mild aortic dilation - Cumulative emotional impact - Progressive functional disability	Decreased quality of life. Psychiatric comorbidities.

* Clinical Evolution of hEDS Across Life Stages. This section details the predominant manifestations at each life stage, from childhood to late adulthood, highlighting clinical progression and functional impact.

In middle and late adulthood, some patients experience a transition toward joint stiffness, reduced hypermobility, and progressive functional decline. This phase necessitates an approach focused on functionality, self-care, and the prevention of comorbidities, with an emphasis on rehabilitation, pain management, and psychosocial support.[31]

Understanding this clinical evolution is essential, as it allows for anticipatin of patient needs and the promotion of person-centered management strategies tailored to each stage of life.

IMPORTANCE FOR PRIMARY AND SECONDARY HEALTH CARE LEVELS

The primary care physician plays a fundamental role in the early identification and initial management of hEDS. When evaluating a young patient presenting with chronic pain, fatigue, joint hypermobility, and multisystemic functional symptoms, the clinician must be prepared to suspect the diagnosis and systematically apply current clinical criteria. This is particularly relevant given the heterogeneous presentation of hEDS, the absence of confirmatory genetic markers, and the limited awareness of low-prevalence genetic diseases, all of which frequently result in underdiagnosis and protracted delayed care.[18,32,33]

The use of the Beighton score, in conjunction with a comprehensive clinical evaluation, facilitates the reduction of underdiagnosis and the coordination of ongoing patient management.[1,13] Additionally, the physician must ensure timely referrals to specialties −including clinical genetics, rheumatology, physical therapy, nutrition, cardiology, neurology, psychiatry, gastroenterology, and dermatology− tailored to the patient's predominant manifestations.[32-34] Orchestrating these multiple specialties enables a holistic approach that addresses both the physical symptoms and the psychosocial impact of hEDS, ensuring continuous and effective care.

In primary care, the systematic monitoring of pain, the judicious use of analgesics, physical therapy, and relaxation techniques are fundamental to patient well-being. Joint stability and injury prevention −achieved through adapted physical activity and education on joint protection strategies− are essential for improving quality of life. Primary care providers also play a pivotal role in patient education and emotional support, thereby mitigating the impact of diagnostic delays. Empathetic, validating, and person-centered care is imperative to minimize the clinical, emotional, and social consequences of the diagnostic odyssey frequently experienced by these patients.

In secondary care, specialists play a critical role in confirming the diagnosis, managing complex complications, and implementing individualized treatment protocols. Effective collaboration among clinical genetics, cardiology, orthopedics, neurology, and rehabilitation services is essential to address multisystemic involvement and prevent life-threatening complications such as aortic aneurysms or spontaneous visceral ruptures. This multidisciplinary model, supported by seamless communication between primary and secondary care levels, is pivotal to providing comprehensive, patients-centered care across all age groups.

The prognosis of hEDS is highly variable and primarily impacts quality of life rather than life expectancy. Unlike the vascular subtype (vEDS), which carries a significant risk of arterial rupture and reduced survival, hEDS rarely compromises longevity.[1,18] However, its heterogeneous presentation −characterized by chronic pain, fatigue, and multisystemic involvement− frequently

lead to functional limitations and profound psychosocial consequences.[4,5,11] Early recognition and multidisciplinary management, including proactive pain monitoring, adapted physical activity, and psychosocial support, can significantly optimize patient outcomes.[4,29-31] Although no curative treatment exists, interventions such as physical therapy, the judicious use of analgesics, and lifestyle modifications are essential to maintain functionality and alleviate symptom burden. In this context, primary care plays a pivotal role in longitudinal follow-up and coordination of specialized care to mitigate disability and enhance quality of life.

CONTINUING MEDICAL EDUCATION

Continuing medical education (CME) is essential to improve the recognition, management, and longitudinal follow-up of rare conditions such as hEDS. Given its clinical complexity and phenotypic variability, healthcare professionals require consistent updates on diagnostic criteria, assessment tools, and interdisciplinary strategies[35] Integrating rare disease content into CME programs facilitates the reduction of diagnostic delays, prevents fragmented care, and strengthens clinical problem-solving capacity. Furthermore, it fosters a culture of informed clinical suspicion, promotes timely referrals to clinical genetics and related specialties, and contributes to more equitable and efficient care for patients with underrecognized conditions. Raising awareness of hEDS and other rare diseases must be a cornerstone of health education strategies, particularly within primary care. This approach not only enhances detection and clinical management but also reinforces the physician-patient relationship, promoting care centered on dignity, respect, and a profound understanding of the patient's lived experience. [35]

CONCLUSIONS

Hypermobile Ehlers-Danlos syndrome (hEDS) represents a significant clinical challenge due to its multisystemic nature, the absence of confirmatory genetic markers, and a high prevalence of underdiagnosis. Nevertheless, it can be accurately identified through meticulous clinical evaluation based on updated diagnostic criteria and a comprehensive, holistic assessment of the patient.

Timely diagnosis can alleviate years of physical and emotional suffering, averting the diagnostic odyssey through multiple specialties and the administration of inadequate symptomatic treatments. Within this framework, the primary care physician plays a pivotal role in early recognition, longitudinal follow-up, and the coordination of a multidisciplinary, person-centered approach.

The quality of life of patients with hEDS can be significantly enhanced when management strategies integrate physical, emotional, and psychosocial interventions. To achieve this, it is imperative to strengthen medical education regarding clinical genetics and connective tissue disorders, particularly within the field of family medicine.

It is recommended to promote educational programs, clinical guidelines, and decision-support tools that bolster knowledge of hEDS starting at the primary care level. Furthermore, encouraging clinical, epidemiological, and psychosocial research is essential to reduce diagnostic delays and optimize comprehensive care for affected individuals.

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