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Hypermobility and Ehlers-Danlos Syndromes in Children Under Five Years of Age

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ABSTRACT

Generalised Joint Hypermobility (GJH) is common in early childhood and reflects the physiological laxity of developing connective tissues. Distinguishing benign hypermobility from Hypermobility Spectrum Disorders (HSD) and Ehlers-Danlos Syndromes (EDS) in children under five is challenging due to developmental variability, limited cooperation with examination and the age dependence of diagnostic criteria. Early recognition of EDS is essential to prevent secondary musculoskeletal complications, optimise motor development and identify children with syndromic or high risk features. This review synthesises current evidence on epidemiology, pathophysiology, clinical manifestations, diagnostic challenges, assessment tools, management strategies and research gaps relating to hypermobility and EDS in young children under 5 years of age. A clearer paediatric specific diagnostic framework is urgently needed to improve early recognition and long term outcomes.

Keywords: Joint hypermobility, Early childhood, Paediatric connective tissue disorders, Beighton score, Developmental delay, Hypotonia, Differential diagnosis, Homocysteinaemia, Homocystinuria

Abbreviations: GJH: Generalised Joint Hypermobility; HSD: Hypermobility Spectrum Disorders; EDS: Ehlers-Danlos Syndromes; JIA: Juvenile Idiopathic Arthritis; ECM: Extracellular Matrix

1. Introduction

Hypermobility in early childhood is common and, in many children, represents physiological laxity rather than disease. Immature connective tissues, reduced muscle tone and ongoing neuromuscular maturation produce a wide range of normal flexibility in children under five and this range varies by age, sex and ethnicity[1]. For clinicians, the central challenge is deciding when joint laxity is an isolated, selflimiting trait and when it is a marker of symptomatic Hypermobility Spectrum Disorder (HSD) or a heritable connectivetissue disorder, most notably an Ehlers-Danlos Syndrome (EDS).

Distinguishing physiological hypermobility from pathological forms is particularly difficult in this age group. Standardised assessment can be limited by cooperation and many features used in current diagnostic frameworks for hypermobile EDS (hEDS)-including chronic widespread pain, recurrent dislocations and some characteristic skin and systemic findings-are agedependent and may not be evident until later childhood or adolescence[2]. As a result, early childhood assessment often relies on careful clinical pattern recognition, identification of redflag features that warrant specialist evaluation and longitudinal followup to clarify trajectory. Early recognition nonetheless matters: timely advice and physiotherapyled interventions can support motor development, reduce injury risk and provide families with appropriate anticipatory guidance, while enabling surveillance and genetic evaluation in children suspected of rarer, higherrisk EDS subtypes. This narrative review synthesises current evidence on epidemiology, mechanisms, clinical manifestations, diagnostic challenges, assessment tools, management strategies and research gaps relating to hypermobility and EDS in children under five, highlighting priorities for developing paediatricspecific diagnostic frameworks.

1.1. Epidemiology of Hypermobility in Early Childhood

Joint laxity is highly prevalent in early childhood and declines with age as connective tissues mature[3]. In a large UK cohort of adolescents, generalised joint hypermobility was present in 27% of girls and 11% of boys, with even higher prevalence expected in younger children[4]. Ethnicity influences baseline flexibility: children of African, Middle Eastern and Asian descent often demonstrate greater physiological laxity, complicating the interpretation of Beighton scores[5].

Before age five, hypermobility is frequently asymptomatic. When symptoms occur, they often include delayed motor milestones, clumsiness or fatigue-features that overlap with normal developmental variation[6]. This overlap contributes to diagnostic uncertainty and delays in recognising children with underlying connectivetissue disorders.

2. Pathophysiology of Hypermobility and EDS

Hypermobility arises from increased elasticity or reduced stiffness of connective tissues, particularly collagen and from the balance between passive ligamentous restraint and active neuromuscular control. In the Ehlers-Danlos Syndromes (EDS), pathogenic variants disrupt collagen synthesis, structure, posttranslational modification or Extracellular Matrix (ECM) assembly, producing multisystem manifestations involving skin, joints, vasculature and internal organs[2]. In addition to primary collagen gene disorders, several metabolic pathways can secondarily influence ECM integrity by altering collagen crosslinking, redox state and methylation capacity-mechanisms that may be relevant in a small subset of children presenting with marked laxity or marfanoid features.

In early childhood, the relative contribution of ligamentous laxity, hypotonia and neuromuscular immaturity complicates the interpretation of hypermobility. The pathophysiology of hypermobile EDS (hEDS) remains incompletely understood, with no confirmed monogenic cause, although familial clustering suggests autosomal dominant inheritance with variable penetrance[5]. Beyond structural gene disorders, onecarbon (folate–methionine) metabolism intersects with connectivetissue biology through regulation of homocysteine and methyldonor availability. Dietary folate (including folic acid) is reduced within the folate cycle and ultimately converted to 5methyltetrahydrofolate (5MTHF), the key methyl donor used (with vitamin B_{12}) for remethylation of homocysteine to methionine. Methionine is then converted to Sadenosylmethionine (SAM), the principal cellular methyl donor for DNA, RNA, proteins and lipids; impaired flux through this pathway can increase homocysteine and alter methylationdependent regulation of ECM gene expression.

Common functional variants in MTHFR (e.g. C677T and A1298C) reduce enzyme activity and can predispose to mild hyper-homocysteinaemia, particularly in the context of low folate or riboflavin status. Although these variants are prevalent in the general population and are not, in isolation, diagnostic of a connectivetissue disorder, raised homocysteine has biologically plausible links to ECM pathology. Experimental work suggests that homocysteine can interfere with collagen maturation by reacting with aldehyde intermediates required for intermolecular crosslink formation, potentially reducing fibril stability and can promote oxidative stress and inflammatory signalling that may influence matrix remodelling. These mechanisms provide a rationale for considering homocysteine as a modifier of tissue resilience rather than a primary explanation for most cases of childhood hypermobility.

More marked disturbances occur in classical homocystinuria due to biallelic CBS (cystathionine βsynthase) mutations, in which trans-sulphuration of homocysteine to cystathionine is impaired, leading to accumulation of homocysteine/homocystine and often methionine. Clinically, CBS deficiency can produce a marfanoid habitus, scoliosis, osteoporosis and joint laxity and may therefore mimic heritable connectivetissue disorders; distinguishing features include ectopia lentis (typically downward), neurodevelopmental involvement and a high risk of thromboembolism. Mechanistically, elevated homocysteine has been associated with reduced collagen crosslinking and abnormal connectivetissue architecture, supporting a metabolic contribution to laxity and tissue fragility in severe hyperhomocysteinaemia[7]. In young children presenting with disproportionate tall stature, lens abnormalities, unexplained thrombosis or a compatible family history, plasma total homocysteine and related metabolic testing should be considered as part of the differential diagnosis alongside genetic evaluation for monogenic EDS subtypes.

3. Clinical Features in Children Under Five

3.1. Musculoskeletal Features

Musculoskeletal manifestations are the most common presenting

features in young children with hypermobility or EDS. These include:

- Delayed grossmotor milestones
- Hypotonia
- Clumsiness or frequent falls
- Joint instability or recurrent softtissue injuries
- Fatigue during play or walking

Hypotonia is particularly prominent in infants with connectivetissue disorders and may contribute to delayed sitting, crawling or walking[8].

3.2. Skin and SoftTissue Features

Skin hyperextensibility, easy bruising and delayed wound healing may be early clues to classical or hypermobile EDS[2]. Atrophic scarring, if present, is highly suggestive of classical EDS. However, many skin features are subtle or absent in early childhood.

3.3. Pain and fatigue

Chronic pain is less common in children under five but may occur in those with significant instability or repeated softtissue trauma[9]. Fatigue may reflect poor proprioception, reduced muscle endurance or compensatory movement strategies.

3.4. Autonomic and Gastrointestinal Features

Some young children exhibit feeding difficulties, reflux, constipation or autonomic dysregulation[10]. These symptoms are nonspecific but may support a syndromic diagnosis when combined with musculoskeletal findings.

4. Diagnostic Challenges and Limitations of Current Criteria

The 2017 international classification of EDS provides detailed criteria for hEDS, but these criteria explicitly exclude children because many features-such as chronic pain, recurrent dislocations and characteristic skin findings-are agedependent[2,11].

Key diagnostic challenges include:

- Developmental variability: flexibility is naturally high in toddlers.
- Limited cooperation: some Beighton manoeuvres are difficult to perform.
- Agedependent features: many diagnostic signs emerge later.
- Overlap with normal development: delayed milestones and clumsiness are common in healthy children.
- Lack of validated paediatric criteria: no consensus exists for diagnosing hEDS in young children.

Redflag features suggesting a monogenic connectivetissue disorder include marked skin fragility, congenital hip dislocation, severe hypotonia, early progressive scoliosis, vascular events or ocular abnormalities[2,12].

5. Importance of Early Diagnosis

Early recognition of EDS in childhood is essential because timely diagnosis enables targeted intervention that can prevent secondary musculoskeletal complications and optimise developmental outcomes. Children with hypermobility or EDS often present with hypotonia, delayed motor milestones, recurrent softtissue injuries and inefficient movement patterns that, if unaddressed, contribute to chronic pain, fatigue and functional impairment later in life[1-3]. Early diagnosis facilitates physiotherapyled strengthening, proprioceptive training and activity pacing, which improve stability and reduce injury risk[3,4,6].

Importantly, identifying EDS early reduces unnecessary investigations and prevents misdiagnosis, particularly in children with bruising, joint dislocations or delayed wound healing, where safeguarding concerns may otherwise be raised[2]. Early recognition of rarer EDS subtypes-such as vascular or kyphoscoliotic EDS-allows appropriate cardiovascular, ophthalmic and spinal surveillance, which can be lifesaving[2]. Early consideration of important metabolic differentials such as homocysteinaemia / homocystinuria is also valuable, as timely diagnosis may prompt thrombosis risk assessment, ophthalmic evaluation and targeted metabolic treatment[13]. Familylevel benefits include genetic counselling, anticipatory guidance and assessment of siblings who may also be affected[11].

5.1. Assessment Tools and Emerging Approaches

The Beighton score remains the most widely used measure of generalised joint hypermobility, but its application in toddlers is limited[7]. Alternative tools, such as the Hospital del Mar criteria or paediatricspecific adaptations, have been proposed but lack widespread validation[14].

Functional assessments-including gait analysis, motorskill evaluation and proprioceptive testing-often provide more clinically meaningful information in this age group. Systemic evaluation should include skin examination, assessment for hernias, spinal alignment and cardiovascular screening when indicated. Genetic testing is reserved for children with features suggestive of rarer EDS subtypes[2].

6. Differential Diagnosis

6.1. Important Differentials Include

Juvenile Idiopathic Arthritis (JIA) should be actively excluded in hypermobile children who present with persistent joint pain, limp or functional decline, because inflammatory arthritis can be misattributed to “growing pains” or mechanical symptoms. Features that should prompt urgent consideration of JIA include objective joint swelling, warmth or effusion; morning stiffness or pain that improves with activity; restricted range of motion; nocturnal pain; systemic features (eg, fever, rash); and persistently raised inflammatory markers (ESR/CRP)[15]. Early paediatric rheumatology referral is recommended when inflammatory features are present, because timely treatment reduces the risk of joint damage and improves outcomes.

Other genetic and neuromuscular differentials include:

- Congenital myopathies
- Metabolic bone disease
- Hypotonic cerebral palsy
- Chromosomal syndromes (e.g., Down syndrome)
- Marfan syndrome
- Loeys–Dietz syndrome
- Homocysteinaemia / homocystinuria[13]

7. Management Strategies

7.1. Physiotherapy and Motor Development

Physiotherapy is the cornerstone of management[16]. Key components include:

- Strengthening of core and proximal musculature
- Balance and proprioceptive training
- Motorskill acquisition
- Activity pacing and fatigue management

Early intervention improves functional outcomes and reduces compensatory movement patterns.

7.1.1. Orthotics and footwear: Supportive footwear and orthotics can improve stability in children with pes planus or ankle instability[17].

7.1.2. Pain management: Pain in this age group is typically managed conservatively with activity modification, physiotherapy and reassurance[9]. Pharmacological interventions are rarely required.

7.1.3. Family education: Parents benefit from guidance on safe play, jointprotective strategies and realistic expectations. Overmedicalisation should be avoided, as most hypermobile children remain active and well[18].

8. Prognosis and LongTerm Outcomes

Most children with benign hypermobility experience improvement as connective tissues mature. However, children with HSD or EDS may develop persistent pain, fatigue, proprioceptive difficulties or functional limitations. Early intervention improves longterm outcomes by reducing injury risk, supporting motor development and preventing maladaptive movement patterns.

9. Research Gaps and Future Directions

Key research priorities include:

- Development of validated paediatric diagnostic criteria
- Improved understanding of the natural history of hEDS in early childhood
- Biomarkers for early identification of connectivetissue disorders
- Longitudinal studies on motor development and functional outcomes
- Evaluation of physiotherapy protocols tailored to young children

A paediatricspecific diagnostic framework is urgently needed to improve early recognition and guide management.

10. Conclusion

Hypermobility in children under five is common and most often reflects normal developmental laxity; however, a clinically important minority have symptomatic Hypermobility Spectrum Disorder (HSD) or an underlying Ehlers-Danlos Syndrome (EDS). In this age group, interpretation is complicated by wide developmental variability, limited cooperation with formal examination and the agedependence of many features used in current diagnostic criteria. Consequently, diagnosis should be framed as a process of longitudinal assessment rather than a single timepoint label.

Clinically, the priority is to identify children who need closer followup or specialist input-particularly those with redflag features (eg, marked skin fragility or atrophic scarring, congenital hip dislocation, severe hypotonia, early progressive scoliosis, vascular or ocular features or a strong family history of a defined connectivetissue disorder). For most symptomatic children, early, developmentally appropriate intervention is beneficial even while diagnostic uncertainty remains. Physiotherapyled strengthening, balance and proprioceptive training, motorskill support and advice on pacing and jointprotective play can reduce injury risk, support participation and help prevent maladaptive movement patterns that contribute to later pain and fatigue. Where indicated, supportive footwear and orthoses may improve function and families benefit from clear anticipatory guidance that avoids both dismissal of symptoms and overmedicalisation.

Earlier recognition also has healthsystem and familylevel benefits, including more efficient referral pathways, avoidance of unnecessary investigations, appropriate safeguarding interpretation when bruising or injury occurs and opportunities for genetic counselling and assessment of relatives when a monogenic subtype is suspected. Looking forward, progress depends on validated paediatric assessment thresholds, prospective studies describing natural history from infancy and trials of earlychildhood physiotherapy and familycentred interventions. Developing and implementing paediatricspecific diagnostic frameworks that integrate joint hypermobility with functional impact and multisystem features is essential to improve timely recognition, guide surveillance for higherrisk phenotypes and optimise longterm outcomes.

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