Paediatric Hypermobility Spectrum Disorder: Neurodevelopmental Considerations

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OUTLINE

- Case Vignette
- Definitions
- Epidemiology
- Pathophysiology
- Evaluation
- Framework for Diagnosis
- Neurodevelopmental considerations
- Management aspects

CASE VIGNETTE

- 24 months old male, presented with history of delayed walking , symptoms of arthralgia on exertion, falling often and speech delay.
- Examination: Not dysmorphic, no myopathic facies, height for age +2SD,
  - Smooth velvety skin, joint hypermobility and ligamental laxity, pes planus, normal palate- no cleft or high-arched palate.
  - Mild hypotonia, normal reflexes and power.
  - Normal cardiac exam
- DA:18 months, (DQ- 76%). Predominantly speech delay – 15 months.
- Labs: Normal CK & TFTs
- Differential Diagnosis: CTD, DCD, HSD, CD

DEFINITIONS

Hypermobility spectrum disorder

- Symptomatic hypermobility-related condition
- Involvement of musculoskeletal complications and at least one other body system and
- **Don't meet hEDS criteria**

Hypermobile Ehlers-Danlos syndrome –

- General features of EDS with less severe manifestations

- **Pediatric generalized joint hypermobility (pGJH)**
  - Joint Hypermobility, **but** no musculoskeletal complications

- **Pediatric generalized hypermobility spectrum disorder (pgHSD)**
  - Joint hypermobility and musculoskeletal complications

Tofts, Louise Jane et al. "Pediatric joint hypermobility: a diagnostic framework and narrative review." *Orphanet journal of rare diseases* vol. 18,1 104. 4 May. 2023, doi:10.1186/s13023-023-02717-2

EPIDEMIOLOGY

- Joint hypermobility is common with 1 in 5 individuals affected.
- **Joint flexibility** is greater during childhood and adolescence and decreases with age.
- Wales cohort study of 6021 individuals a combined prevalence of hEDS and HSD of 1 in 500 and 1 in 3200 of hEDS specifically. (Demmler JC et al BMJ Open. 2019.)

- Combined prevalence of HSDs and hEDS is 1 in 600 to 1 in 900 respectively (systematic review Carroll et al-Carroll, *Rheumatology and immunology research* 2023)
  - The mean age at diagnosis in men peaked at 9.5 years while women was 14-19 years with 72% of men diagnosed in childhood.

PATHOPHYSIOLOGY

- Underlying molecular pathophysiology of HSD and hEDS is unknown.
- No structural abnormality in collagen or related proteins Identified
- Dominant inheritance pattern
- Biomechanical overloading/soft tissue injury due to joint laxity/instability.
- Associated co-morbid conditions play a role in the pathogenesis

HISTORY

- **Infancy**
  - As early as birth, hypermobility symptoms may be seen e.g. congenital hip dislocation
  - Hypotonia
  - Delayed motor development

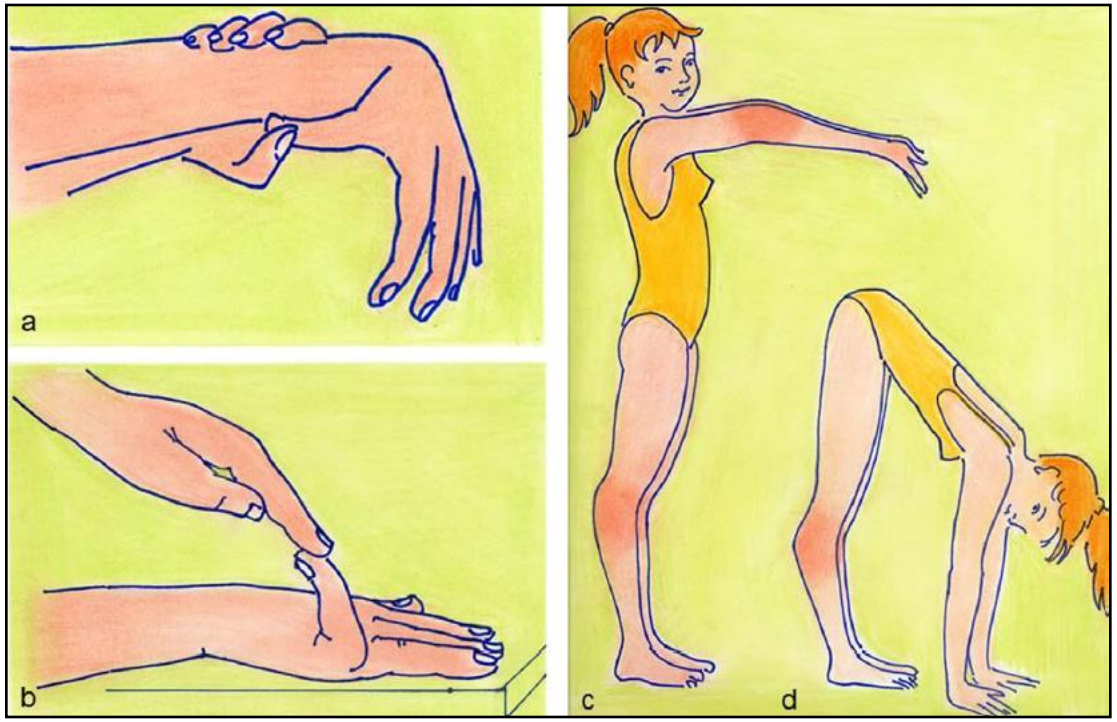
- **Early Childhood**
  - Clumsiness especially in early childhood
  - Early childhood history of excessively flat feet and knock knees.
  - Common/increasing complaints of persistent MSK pain especially during periods of intense play/activity (commonly recurrent foot, ankle and knee pains)
  - Difficulty participating in sports and physical activities
  - Recurrent joint dislocations/subluxations

- **School going/Adolescence**
  - Problems with handwriting
  - Back/hip pain especially in adolescent years.

- **Functional GI complaints, urinary incontinence and anxiety.
    - **Joint Pain**
    - **Fatigue.**
    - **Functional GI D/O**
    - **Dysautonomia**
    - **Anxiety**

CLINICAL FINDINGS

Joint hypermobility



. Musculoskeletal complications

Poor proprioception, coordination difficulties,
Ligament and tendon injuries
Dislocations
Subluxations

+/- Skin (seen in hEDS)

- Soft smooth skin, stretchy skin
- Atrophic scars
- Bruises

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Colombi, et al (2015). Differential Diagnosis and Diagnostic Flow Chart of Joint Hypermobility Syndrome/Ehlers-Danlos Syndrome Hypermobility Type Compared to Other Heritable Connective Tissue Disorders. American Journal of Medical Genetics Part C:.

DIAGNOSTIC FRAMEWORK FOR PEDIATRIC JOINT HYPERMOBILITY

		Generalized Joint hypermobility	Skin and tissue abnormalities	Musculoskeletal complications	Core comorbidities
Asymtomatic	Pediatric generalized joint hypermobility (pgJH)	Present	Absent	Absent	Absent
	pgJH with skin involvement	Present	Present	Absent	Absent
Symptomatic	pgJH with core comorbidities	Present	Absent	Absent	Present
	pgJH with core comorbidities and with skin involvement	Present	Present	Absent	Present
	Pediatric hypermobility spectrum disorder (pgHSD), musculoskeletal subtype	Present	Absent	Present	Absent
	pgHSD subtype with skin involvement	Present	Present	Present	Absent
	pgHSD, systemic subtype	Present	Absent	Present	Present
	pgHSD, systemic subtype with skin involvement	Present	Present	Present	Present

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Diagnostic criteria for pediatric joint hypermobility

Paediatric Working Group
The International Consortium on Ehlers-Danlos Syndromes & Related Disorders
In Association with The Ehlers-Danlos Society

Diagnostic criteria for pediatric joint hypermobility

This diagnostic checklist is to support doctors to diagnose pediatric joint hypermobility and hypermobility spectrum disorder

Distributed by The Ehlers Danlos Society.

Patient name:_____ DOB:_____ DOV:_____ Evaluator:_____

Chidren from 5 years of age until biological maturity

L☐R☐ L☐R☐ L☐R☐ L☐R☐ ☐

Beighton score:____/9
Must be a minimum of 6

Skin and tissue abnormalities

- ☐ Unusually soft skin – unusually soft and/or velvety skin
- ☐ Mild skin extensibility
- ☐ Unexplained striae distensae or rubae at the back, groin, thighs, breasts, and/or abdomen without a history of significant gain or loss of body fat or weight
- ☐ Atrophic scarring involving at least 1 site and without the formation of truly papyraceous and/or hemosideric scars as seen in classical EDS
- ☐ Bilateral piezogenic papules in the heel
- ☐ Recurrent hernia, or hernia in more than 1 site (excludes congenital umbilical hernia)

Score:____/6
Must be a minimum of 3

Musculoskeletal complications

- ☐ Episodic activity related pain not meeting the chronic pain frequency and duration criteria
- ☐ Recurrent joint dislocations, or recurrent subluxations in the absence of trauma, and/or frank joint subluxation on physical exam in more than 1 joint (excludes radial head <2 years)
- ☐ Soft tissue injuries – 1 major (needing surgical repair) and/or current multiple minor tendon, and/or ligament tears

Score:____/3
Must be a minimum of 2

Comorbidities

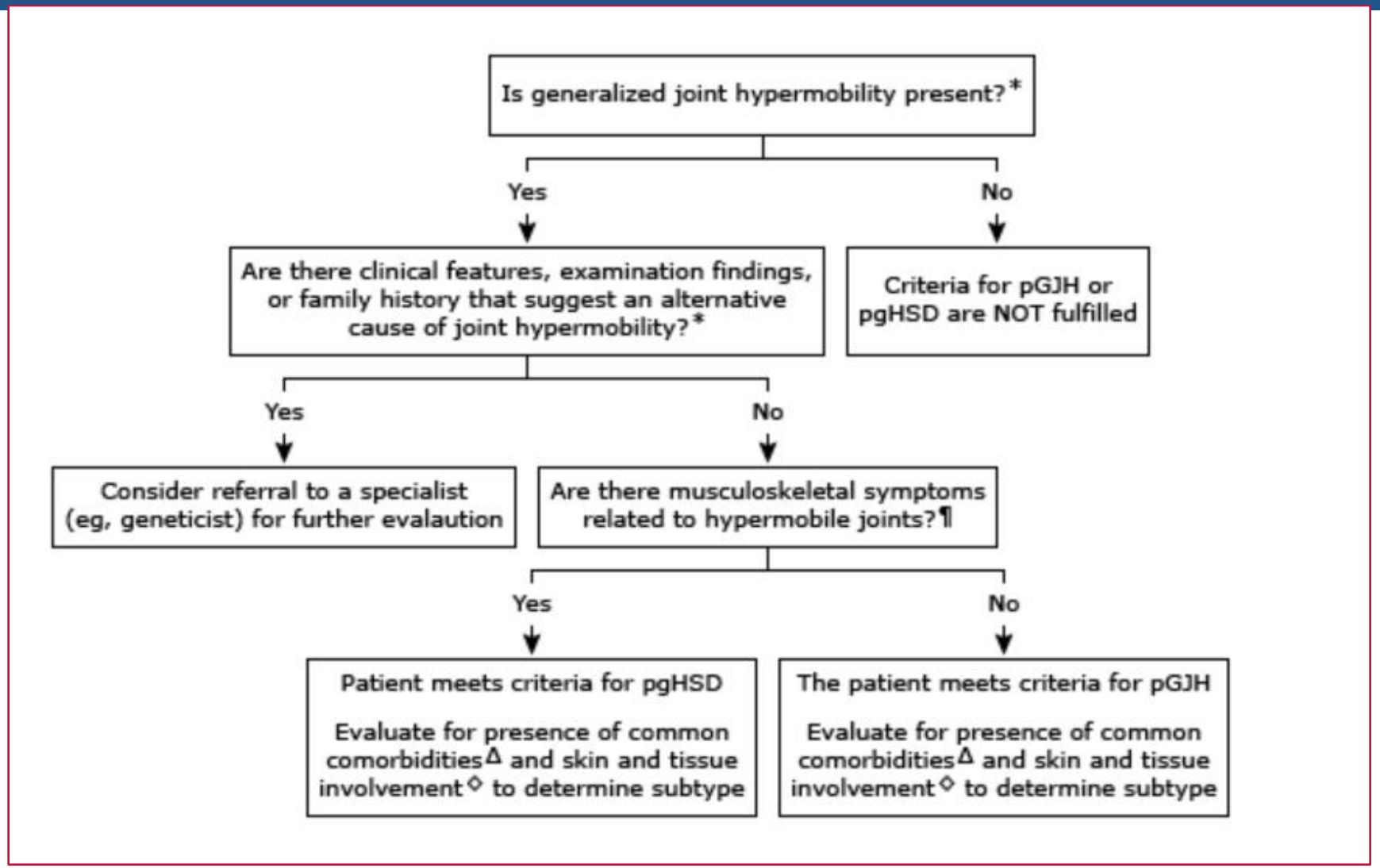
- ☐ Chronic primary pain
- ☐ Chronic fatigue
- ☐ Functional GI disorders
- ☐ Functional bladder disorders
- ☐ Primary dysautonomia
- ☐ Anxiety

Any number causing distressor disability?
Y/N

A diagnostic checklist for pediatric joint hypermobility and hypermobility spectrum disorder

Tofts, Louise Jane et al. “Pediatric joint hypermobility: a diagnostic framework and narrative review.” *Orphanet journal of rare diseases*

EVALUATION OF pGJH & pGHSD



DIAGNOSTIC EVALUATION

- No confirmatory test for HSD or hEDS, diagnosis is clinical.
- Important to rule out the more severe forms of EDS or
- Rule out other Connective Tissue diseases

- Examine for systemic involvement
  - e.g. cardiac echo to exclude Cardiac valve disease, congenital heart disease, mitral valve prolapse, aortic dilatation
- Link to genetic testing if other systems involved
  - E.g blue sclera, lens dislocation

MANAGEMENT

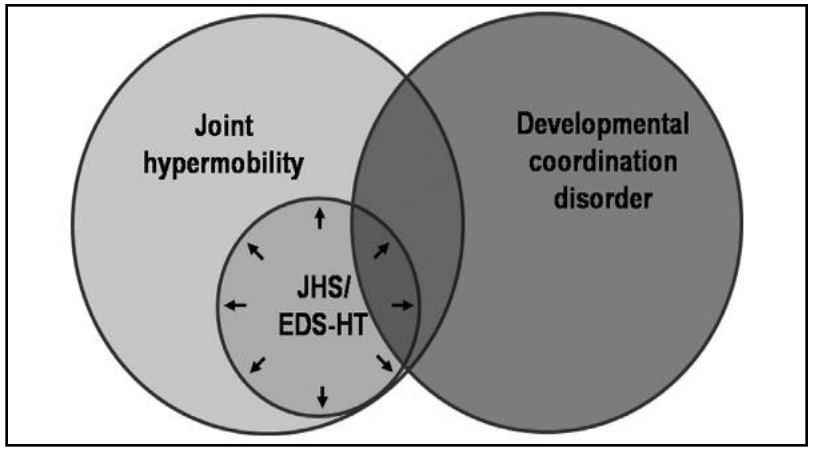
- **Multidisciplinary Team Management Approach (MDT)**
- Rheumatology, genetics, Orthopedics, physiotherapy, occupational therapy
- Neurodevelopmental if DD.
- **Education**: Teachers must be aware and supportive.
- **Physical education**: Coaches must be educated on condition and avoid overexertion
- Appropriate mgt of pain, functional and psychiatric d/o appropriately and referral if necessary.

NEURODEVELOPMENTAL CO-MORBIDITIES IN CHILDREN & ADOLESCENTS WITH HSD

- Developmental Co-ordination Disorder (DCD)
- Attention Deficit Hyperactivity Disorder (ADHD)
- Autism Spectrum Disorder (ASD)
- Learning Disorders (LD)
- Communication Disorders (CD)

DEVELOPMENTAL COORDINATION DISORDER (DCD)

- Higher prevalence of DCD vs other NDDS in JHM/HSD
- Symptom overlap



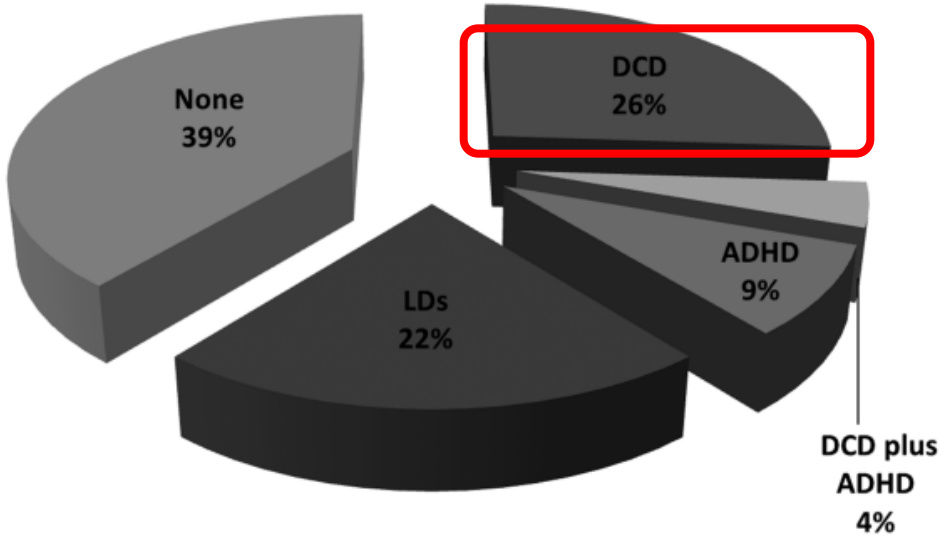
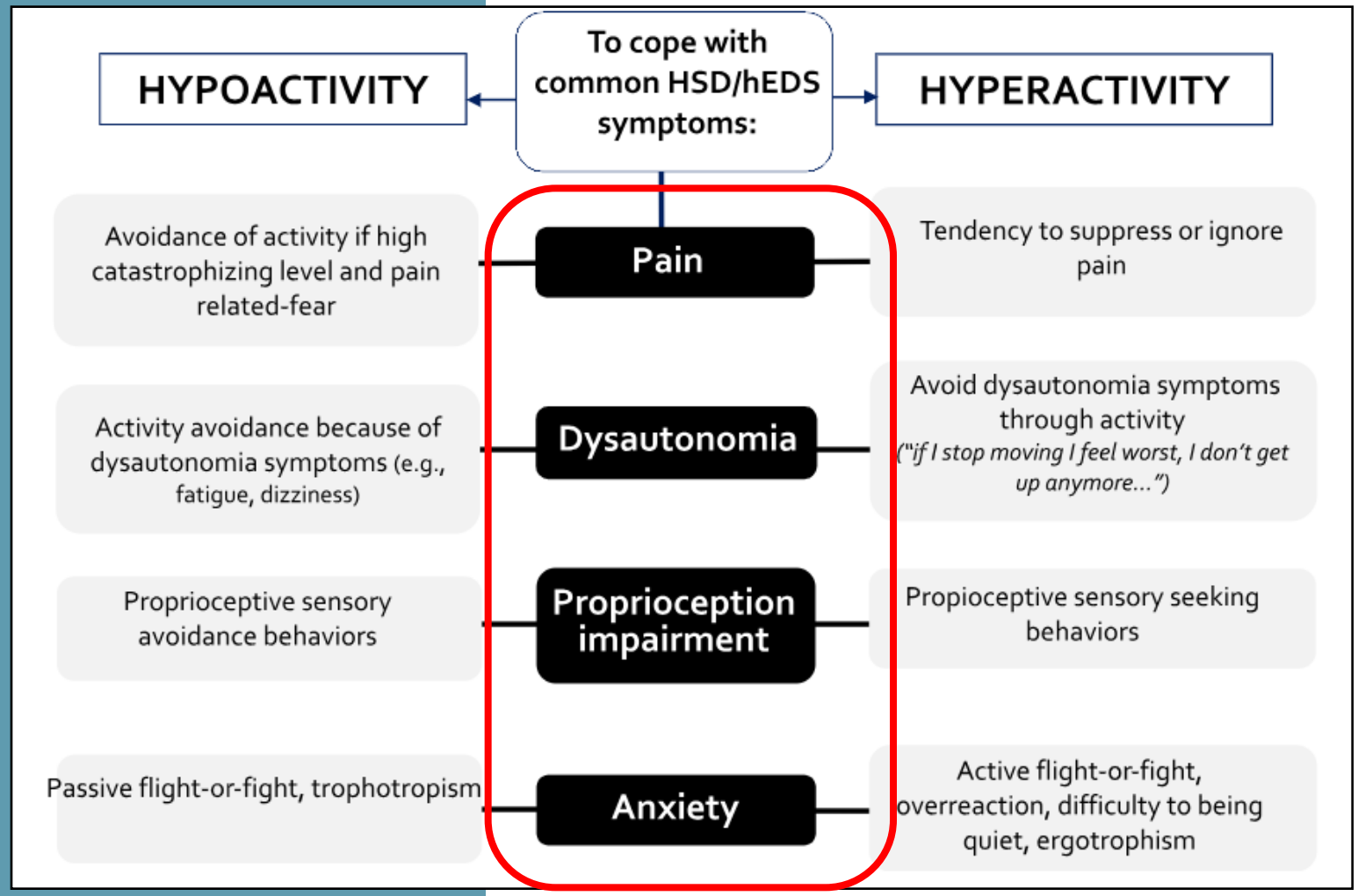


FIGURE 1 Graphical summary of the neurodevelopmental comorbidities in the 23 pediatric patients with HCTDs (Group 1). ADHD = attention deficit-hyperactivity disorder; DCD = developmental coordination disorder; HCTD = hereditary connective tissue disorder; LDs = learning disabilities

Piedimonte C, et al Exploring relationships between joint hypermobility and neurodevelopment in children (4-13 years) with hereditary connective tissue disorders and developmental coordination disorder. Am J Med Genet B Neuropsychiatr Genet. 2018

ATTENTION DEFICIT HYPERACTIVITY DISORDER

Common features in HSD/EDS that may favor hyperactivity and hypo activity



Baeza-Velasco C. Neurodevelopmental atypisms in the context of joint hypermobility, hypermobility spectrum disorders, and Ehlers-Danlos syndromes. Am J Med Genet C Semin Med Genet. 2021 Dec

AUTISM SPECTRUM DISORDER

Maximum passive joint motility (angle) comparing children with autism spectrum disorders and their individually matched controls (typically developing peers).

Passive joint motility	Children				*P* value
	With autism spectrum disorders		Typically developing peers		
	Mean degrees	(s.d.)	Mean degrees	(s.d).	
Finger flexion	120	15.6	93	16.1	<.0001
Finger extension	118	15.5	83	21.3	<.0001
Wrist flexion	132	17.7	101	16.8	<.0001
Wrist extension	115	15.2	87	15.8	<.0001
Elbow flexion	153	10.1	143	9.6	.0002
Elbow extension	26	10.0	11	7.2	<.0001
Ankle planti-flexion	39	13.3	31	12.4	.002
Ankle dorsi-flexion	87	15.2	61	15.1	<.0001

Overlap of symptoms ? Genetic Milieu ? Brain heterotopia

Assess for JHM/HSD associated complaints in ASD individuals

Consider physical interventions for JHM to improve function

Shetreat-Klein M, et al Abnormalities of joint mobility and gait in children with autism spectrum disorders. Brain Dev. 2014 Feb

LEARNING DIFFICULTIES

- Learning difficulties overrepresented among hypermobility-related disorders. (14%)

Associated symptom/feature	Proportion (%)
Pain exacerbated by exercise	80/99 (81)
Pain exacerbated by infection	30/83 (39)
Infection at beginning of symptoms	22/86 (26)
School missed	42/102 (41)
Problems at school	21/88 (24)
Handwriting problems	42/106 (40)
PE missed	49/103 (48)
Sport hobbies	35/52 (67)
Wheelchair/crutches used	27/107 (25)
Benefits applied for	12/69 (17)
Benefits received	7/69 (10)

Associated clinical feature	Proportion (%)
Congenital dislocatable hips (CDH)*	4/103 (3.9)
Clicky hip	12/103 (12)
Walked after 15 months	19/57 (33)
Poor coordination	30/86 (36)
Clumsy	44/92 (48)
Learning difficulty	13/91 (14)
Dyslexia	2/88 (2)
Dyspraxia	6/87 (7)
Hernias	4/101 (4)
Constipation	9/85 (11)
UTI	
Females*	7/53 (13)
Males*	3/51 (6)
Urinary tract dysfunction (Vesico-ureteric reflux 3, urge-incontinence 1)	4/99 (4)
Heart murmur	5/104 (5)
Easy bruising	39/91 (43)
Clicky joints	25/84 (30)
Joint laxity in 1° relative	57/90 (63)

*Significantly higher result than for normal population.

- N. Adib, K. Davies, R. Grahame, P. Woo, K. J. Murray, Joint hypermobility syndrome in childhood. A not so benign multisystem disorder?, *Rheumatology*, Volume 44, Issue 6, June 2005

COMMUNICATION DISORDERS

Comparison Between the Hypermobile (DCD-H) and Non-Hypermobile (DCD-NH) Groups of Children with DCD

Feature	DCD-NH (Total – 22)	DCD-H (Total – 19)	*P*-value
Gender	M = (17) 77%; F = (5) 23%	M = 14) 73%; F = (5) 27%	0.92
Age	79 months (± 33 months)	87 months (± 33 months)	0.23
Cesarean delivery	1 (4%)	3 (16%)	0.495
Prematurity	1 (4%)	2 (10%)	0.895
Birth problems	5 (23%)	5 (26%)	0.922
Plagiocephaly	1 (4%)	0	0.941
Crooked feet	0	1 (5%)	0.941
Congenital hip dysplasia	0	3 (16%)	0.182
Neonatal UTI	2 (9%)	2 (10%)	0.709
Delayed toddling	11 (50%)	5 (26%)	0.219
Tiptoe walking	1 (4%)	5 (26%)	0.128
Delayed ambulation	15 (68%)	11 (58%)	0.721
Clumsiness	14 (64%)	17 (89%)	0.119
Painful pronation	0	2 (10%)	0.405
Learning difficulties	5 (23%)	9 (47%)	0.184
Language delay	17 (77%)	12 (63%)	0.518
Abdominal hernias	0	4 (21%)	0.082
Frequent falls	4 (18%)	18 (95%)	**<0.001**
Bruising and prolonged bleeding	0	14 (74%)	**<0.001**
Motor impersistence	5 (23%)	17 (89%)	**<0.001**
Sore hands from writing	2 (9%)	10 (53%)	**0.007**
ADHD	8 (36%)	17 (89%)	**0.002**
Constipation	0	10 (53%)	**<0.001**
Arthralgias/myalgias	1 (4%)	11 (58%)	**<0.001**

Celletti C, et al F.. Am J Med Genet C Semin Med Genet. 2015 Mar.

COMMUNICATION DISORDERS

Speech and Language Results in the Hypermobile (DCD-H) and Non-Hypermobile (DCD-NH) Groups of Children with Developmental Coordination Disorder.

Feature	DCD-H	DCD-NH	χ^2	*P*-value
Gender	14 males; 5 females	17 males; 5 females	0.07	0.78
Language disorders	12/19	16/22	0.43	0.51
Type of language disorder				
Expressive	4/12	8/16	0.78	0.37
Phonological	2/12	3/16	3.07	0.88
Receptive/expressive	6/12	5/16	0.78	0.31
Narrative difficulties	14/19	7/22	7.15	**<0.001**
Atypical Swallowing	14/19	4/22	12.75	**<0.001**

Celletti C, et al F.. Am J Med Genet C Semin Med Genet. 2015 Mar.

MANAGEMENT ASPECTS

- Family Counseling
- Promote regular physical activity; improve proprioception
- Caution regarding contact sports and activities with high risk of joint trauma.
- Educational support
- Referral to clinical psychology/psychiatry for co-morbidities e.g. depression, anxiety
- Incorporate sensory integration approaches in physiotherapy.

CONCLUSIONS

- Presence of JHM in children warrants assessment for comorbidities
- Common association of JHM with NDDs
- JHM comorbidities may compound NDD problems
- JHM/HSD mgt strategies must be put into consideration in interventions for NDDs

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Thank you for Listening