

Maroteaux-Lamy syndrome (Mucopolysaccharidosis type VI): symptoms and the impact on function and activities of daily living (ADL)

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BACKGROUND

- Mucopolysaccharidosis type VI (MPS VI), also known as Maroteaux-Lamy syndrome, is a rare autosomal recessive, inherited lysosomal storage disorder caused by a deficiency of *N*-acetylgalactosamine 4-sulfatase.¹
- Insufficient enzyme levels prevent the degradation of carbohydrates called glycosaminoglycans (GAGs), resulting in GAG accumulation and subsequent physical manifestations of the disease.¹
- MPS VI is a clinically heterogeneous disease with a wide range of disease progression, severity of symptoms, and affected organ systems.
- Patients with MPS VI receiving approved IV enzyme replacement therapy (ERT) continue to report ongoing stiffness,² pain,^{3,4,5} inflammation,⁶ and heart and airway soft tissue manifestations.^{7,8,9}

OBJECTIVES

To identify the most important and relevant symptoms experienced by pediatric patients with MPS VI currently receiving ERT, and to identify the best way to measure these symptoms in clinical trials of new treatments for MPS VI.

METHODOLOGY

- A targeted review of MPS VI published literature and clinicaltrials.gov was conducted to:
 - define disease characteristics and clinical outcome assessments (COAs) used in MPS.
 - determine applicability of COA items to key MPS VI disease characteristics.
- The National MPS Society assisted with recruitment of MPS VI patients and their caregivers to participate in a focus group.
- All patients/caregivers assented/consented to participate and the focus group was audio recorded. De-identified information was provided to the sponsor.
- Patients and caregivers were asked a series of polling questions and open-ended questions to elicit a comprehensive understanding of the range of impairments present and the impact on activities of daily living.
- Patients ≥ 8 years and all caregivers participated in cognitive debriefing, completing sample Patient Reported Outcome questionnaires (PROs) and describing their thought process/interpretation as they answered each question. Probes explored relevance and ease, choice of answers, interpretation and meaning of questions.

Patient-Reported Outcomes (PROs)

The following COAs, which have available normative data, were reviewed by the focus group.

- Pediatric Outcomes Data Collection Instrument (PODCI)**¹⁰
 - <https://www.aaos.org/research/outcomes/Pediatric.pdf>
 - Designed for children age 2-10 (parent proxy) and 11-18 with general health problems, specifically bone and muscle conditions. 5 Scales: Upper Extremity and Physical Function; Transfer and Mobility; Sports and Physical Function; Pain; Comfort and Happiness
- Patient Reported Outcome Measurement Information System® (PROMIS®)**¹¹
 - <http://www.healthmeasures.net/explore-measurement-systems/promis/intro-to-promis>
 - Evaluates physical, mental and social health in adults and children, includes parent proxy, across all conditions
 - Domains most relevant to MPS VI are Fatigue; Pain Severity, Interference and Behavior; Mobility, and Upper Extremity Function
- Pegboard Dexterity Test**¹²
 - Focus group patients also completed a pilot NIH Pegboard Dexterity Test, a simple test of manual dexterity that records the time required for participants to accurately place and remove nine plastic pegs into a plastic pegboard
 - Recommended for ages 3-85

RESULTS

- The focus group included 9 patients (8/9 female) diagnosed with MPS VI receiving ERT aged 4-18 years.
- 2 patients presented with slowly progressing MPS VI.
- One caregiver attending was male, the remainder female.

Overall Function

Participants were asked to rank 1st-4th most challenging; the first 2 most challenging are presented

- 33.3% of patients/caregivers cited mobility and independence (each) as their most challenging, with over half citing mobility as most or 2nd most challenging
- Fine motor tasks were reported by 78% as the most or 2nd most challenging
- 33.3% of patients/caregivers cited sleep as most or 2nd most challenging

Table 1. Polling Question: What aspects of MPS VI do you find the most bothersome or challenging for your child?

Questions	Most Challenging	2 nd Most Challenging
Mobility including ambulation and stairs	3 (33%)	2 (22%)
Independence in dressing and using the bathroom	3 (33%)	0
Fine motor tasks like writing, using a computer key board or grasping small items	1 (11%)	6 (67%)
Sleep	2 (22%)	1 (11%)
Fatigue	0	
Total	9	9

Mobility

Table 2. Polling Question: Which mobility tasks are the most challenging for your child?

Questions	Most Challenging	2 nd Most Challenging	3 rd Most Challenging
Running short distances	1 (12.5%)	5 (62.5%)	
Walking on uneven surfaces	1 (12.5%)	1 (12.5%)	2 (33.3%)
Walking longer distance >1-2 blocks	6 (75%)	1 (12.5%)	1 (16.7%)
Transition from floor to stand	0	1 (12.5%)	3 (80%)
Walking up and down a flight of stairs without a handrail	0	0	0
Total	8	8	6

The following challenges were raised in addition to the polling questions through interactive discussion: 86% reported use of furniture or assistance for floor to stand, 56% need assistance for stairs, and 11% described shortness of breath with ambulation. All patients/caregivers endorsed mobility as having a key impact on activities of daily living. None of the patients were able to participate in regular physical education at school and only one patient/caregiver endorsed the ability of their child to run.

Arm and Hand Function

- All patients had experienced carpal tunnel syndrome and several patients had undergone surgical repair.
- Patients employed multiple strategies while writing with a pen or pencil such as self-limiting writing and taking breaks, switching hands. Quality of writing deteriorated over time.
- 8/9 patients/caregivers reported decreased shoulder range of motion that presented in the preschool years, and continued to the present day.
- Caregivers reported that children had developed compensatory strategies to get arms higher such as overextending the spine.

Table 3. Polling Question: Which of the following upper extremity activities are the most challenging for your child?

Questions	Caregiver	Child
Pouring a drink from a full pitcher or carton	0	2 (28.5%)
Opening a jar by him or herself	4 (50%)	2 (28.5%)
Lifting or reaching for a heavy item overhead	4 (50%)	3 (42.9%)
Using a key to open a lock		0
Write with a pen or pencil		0
Total	8	7

Dressing

- The majority of participants/caregivers discussed that taking a shirt off was more difficult than putting on a shirt due to reduced shoulder range of motion.
- Challenges were experienced with putting on pants, zipping and buttoning and putting on and zipping up a coat. Clothing adaptations (avoiding zippers, buttons) enabled greater independence.
- Putting on shoes sometimes caused wrist pain, and patients reported difficulty grasping the shoe adequately and managing laces due to fine motor limitations.

Pain

- Pain was specifically explored to understand presence and impact on disease management and activities of daily living. One caregiver identified pain as the biggest challenge, and 6 caregivers as the 2nd biggest challenge in management of MPS VI.
- Patients/caregivers endorsed the presence of pain in hands, wrists, shoulders, knees, hips, and back.

Table 4. Polling Question: Pain

	Adult: Pain limits my child's ability to complete schoolwork	Adult: Pain limits my child's ability to fall or stay asleep at night	Child: Pain limits my ability to fall or stay asleep at night	Adult: Pain limits my child's participation in sports and recreational activities
Never	3 (36%)	2 (25%)	1 (17%)	2 (22%)
Almost never	1 (12%)	0	1 (17%)	0
Sometime	3 (36%)	5 (68%)	3 (50%)	4 (44%)
Almost always	1 (12%)	0	0	2 (22%)
Always	0	1 (12%)	1 (17%)	1 (11%)
Total	8	8	7	9

Fatigue

- All patients/caregivers noted that fatigue was present and impacted activities of daily living. Many patients took rests or naps or discontinued/modified activities due to an inability to keep up or complete tasks.
- Caregivers noted that their children may continue to participate in the activities but experienced significant fatigue or pain following the activity.
- Key considerations related to fatigue were shortness of breath with ambulation (1 patient), worsening fatigue with weather changes (2 patients) and that posture changes with increased fatigue (1 patient).

COA Endorsement

PODCI

- Patient/caregivers found the items on the PODCI easy to understand and to provide a good picture of function, endorsing the ambulation items and the focus on sports, recreational activities and physical education in school, as well as dressing and social impact.

- Focus group sample data demonstrate that the PODCI had a ceiling effect for the youngest patient in the group with baseline values that fall within one standard deviation from the normative mean. In the Transfer and Basic Mobility Scale, the Sports and Physical Function Scale and the Global Functioning scale, the majority of the participants had normative mean values at least 2 SD below the normative mean.

- Some items were considered to be less relevant to preschool age children such as lifting heavy books and pouring a half-gallon of milk. Caregivers liked that the response items included a choice for "too young for this activity."

PROMIS Pediatric

- All mobility bank v2.0 items were endorsed by at least 7/9 patients/caregivers except the items "my child can move his or her legs" and "stand up on tiptoes".

- All Pain Interference and Behavior items were endorsed as relevant to their children, as well as easy to understand and answer.

NIH Peg Dexterity Test

- All patients displayed the ability to pick up the pegs, place and remove the pegs, however, it took longer to complete the test than the normal mean time by age.
- 6/9 patients demonstrated a pronated grasp (arm and hand posture turned inward) instead of a pincer grasp and used multiple compensatory strategies.

SUMMARY AND ENDPOINT COA RECOMMENDATIONS

Table 5. Recommended COAs

Impairment ¹³	Functional Impact	COA
• Bony abnormalities	• ↓ Range of motion; restricts overhead reach and dressing	• PROMIS Upper Extremity, PODCI Upper Extremity Scale
• Pain	• ↓ Dexterity in dressing, eating and academic tasks	• NIH Tool Box- Pegboard Dexterity test
• Stiffness	• Gait inefficiencies and decreased functional mobility	• 2MWT ¹² /6MWT ¹⁴
• Weakness	• Spinal abnormalities can impact symmetry, respiration, overhead reach	• Timed Stair Climbing Task
	• Pain → further reduces function	• PROMIS Pain Severity, Interference and Behavior
	• Surgical correction may be necessary → post op recovery	• PODCI Pain and Comfort
		• Grip Strength
• Short Stature	• Impacts social acceptance and peer relationships	• PODCI Sports and Physical Function Scale
	• Makes mobility more difficult, especially over long distances and climbing stairs	
	• Impacts recreational opportunities	
• Cervical Spinal Cord Compression	• ↓ sensation and fine motor function in hands	• PODCI Upper Extremity Scale and PROMIS Upper Extremity
• Carpal Tunnel Syndrome	• Pain	• PROMIS Pain Severity, Interference and Behavior
	• Impacts sleep	• PODCI Pain and Comfort Scale
	• ↑ Academic fine motor limitations	• NIH Tool Box-Pegboard Dexterity Test
• Cardiac and Pulmonary Abnormalities	• ↓ Endurance	• 2MWT/6MWT
	• ↑ fatigue, breathlessness and sleep apnea	
	• Heart disease and airway obstruction are major causes of death	
• Decreased Hearing and Vision	• Impacts mobility and ADL in school community and home environment	• None of the tests require visual acuity or extensive verbal direction. All 9 patients in the pilot were able to complete the peg test

- The focus group endorsed key mobility limitations as transitions from floor to standing, stairs, getting up from the toilet, getting into bed and walking distances longer than 1-2 blocks.
- Upper extremity function was endorsed as a key challenge in all patients. Overhead reach, lifting heavier items, and tasks that involve use of pincer grasp or whole hand grasp were found to be the most problematic. Dressing was endorsed as a major challenge.
- Pain was present in all patients and impacted mobility, upper extremity function, dressing, academics, peer interaction and community sports and recreation. These results support previous research that suggests that pain in MPS is underestimated.¹⁵
- Patients with classic MPS VI had greater severity of bony abnormalities than slowly progressing patients, and more restricted range of motion and stiffness. Pain also impacted range of motion.
- All patients experienced fatigue as a symptom that impacted on the engagement in activities of daily living.

Disclosures

Sharon Charles and Melanie Duiker are employees and stockholders of Paradigm Biopharmaceuticals Limited. Dawn Phillips, Beth Leiro, and Paul Harmatz are consultants to Paradigm Pharmaceuticals Limited. Paradigm Biopharmaceuticals Limited sponsored this research.

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