

Exploring the Journeys of Patients with Mucopolysaccharidosis Type VI and Their Family Members at a Tertiary Care Hospital in Saudi Arabia: A Mixed-Methods Case Study

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Abstract

Background

Mucopolysaccharidosis type VI (MPS-VI) is a rare inherited lysosomal storage disorder caused by deficiency of arylsulfatase B. In Saudi Arabia, the prevalence of MPS-VI is substantial owing to high consanguinity rates, leading to significant clinical, psychosocial, and economic burdens on affected families and the healthcare system. Given the challenges posed by RDs, improved access to ODs is crucial. This study explored the diagnostic pathway, treatment experiences, and care coordination challenges of patients with MPS-VI treated at a tertiary care hospital.

Methods

A sequential explanatory mixed-methods approach was used. In the quantitative phase, clinical data were extracted retrospectively from Electronic Medical Records for patients with MPS-VI receiving Galsulfase, Enzyme Replacement Therapy. In the qualitative phase, semi-structured interviews were conducted with the MPS-VI patients' family members to contextualise the clinical findings. Quantitative data were summarised descriptively, and qualitative data were analysed thematically.

Results

Nine patients participated in the quantitative studies, and seven of them participated in semi-structured interviews. Anthropometric measures improved after enzyme replacement therapy, with an average height increase of 17.2 cm, and most patients with comparable measurements showed improved functional endurance, as evidenced by a 75-m gain in the 6-minute walk test. The average time from symptom onset to diagnosis was approximately 24 months, and treatment delays were common. Four qualitative themes were identified: Diagnostic and Care Provision Inequities; Treatment Pathways and Continuity of Therapy; Logistical Burdens and Care Coordination Gaps; and Psychosocial and Emotional Strain.

Conclusion

Overall, this study's findings highlight the clinical benefits of Enzyme Replacement Therapy, as it enhanced growth and functional endurance. However, diagnostic delays, treatment interruptions, and psychosocial family burdens remained. Early recognition, streamlined referral and procurement processes, coordinated multidisciplinary care, and stronger psychosocial support may improve MPS-VI care in Saudi Arabia

Background

Mucopolysaccharidosis type VI (MPS-VI), also known as Maroteaux–Lamy syndrome, is a rare, autosomal recessive lysosomal storage disorder (LSD) caused by arylsulfatase B deficiency, which results in intracellular accumulation of dermatan sulfate (DS) and chondroitin sulfate in cells and tissues.⁽¹⁾ Notably, this accumulation leads to progressive multi-systemic complications^(2, 3) that significantly exacerbate morbidity and reduce life expectancy.⁽¹⁾ The clinical manifestations of MPS-VI vary in severity and may include growth impairment, skeletal abnormalities⁽⁴⁾, cardiac and pulmonary involvement⁽⁵⁾ and vision and hearing loss.^(2, 6–9) Unlike other MPS subtypes, cognitive function is typically preserved in MPS-VI, enabling a more accurate assessment of physical disease burden.^(3, 10, 11)

The severity of MPS-VI depends on various factors, including age at onset, residual enzyme activity, and urinary glycosaminoglycan (uGAG) levels.⁽¹²⁾ Reportedly, patients with a rapidly progressing phenotype show uGAG levels of > 200 µg/mg, exhibiting severe systemic issues and mortality risk due to cardiac or respiratory failure before reaching adulthood.^(4, 13) In contrast, those with the milder phenotype, displaying lower uGAG levels,⁽¹³⁾ present the life expectancy of up to their 40s or 50s.^(5, 14) Consequently, early diagnosis and timely intervention are critical for improving patients' clinical outcomes.

Globally, MPS presents an estimated prevalence of 1 case per 16,000–30,000 births.^(15–17) In SA, although there are no national registry data for MPS-VI, a retrospective study from the Eastern Province (1983–2016) on LSD incidence reports MPS-VI to be the most common MPS subtype, exhibiting a birth prevalence of 14 per 100,000 live births⁽¹⁸⁾ with additional data suggesting a nationwide estimate of 7.85 per 100,000 live births.^(17, 19) These statistics suggest that SA has one of the highest reported MPS-VI rates globally. This high incidence rate may be attributed to the high prevalence of CMs, a well-documented risk factor for genetic disorders in SA.⁽¹⁷⁾ The reported high burden highlights the need for improved genetic screening, early diagnosis, and better resource allocation for rare disease (RD) care in SA.

Caring for individuals with MPS-VI requires a coordinated, multidisciplinary approach⁽⁴⁾ involving orthopaedic specialists, cardiologists, pulmonologists, physiotherapists, and allied health professionals for effective management of complications, supporting joint mobility, and optimising the quality of life.⁽²⁰⁾ Although no definitive cure exists for MPS-VI, present management focuses on Enzyme Replacement Therapy (ERT) with Galsulfase, a recombinant form of human N-acetylgalactosamine 4-sulfatase, which reduces glycosaminoglycan accumulation⁽²⁰⁾, thereby improving endurance, pulmonary function, and mobility.^(21–24) However, ERT alone does not elicit sufficient results, necessitating additional symptomatic and supportive treatments tailored to the involved organ systems based on individual clinical needs.^(6, 25) Although long-term outcomes remain elusive, ERT has demonstrated notable clinical benefits in both trials and real-world settings.⁽²⁶⁾ Studies on MPS-VI focus on overall management, stabilisation of disease progression, preservation of functional independence, and improvement in patient well-being through timely intervention and ongoing multidisciplinary support.⁽²⁵⁾

Nevertheless, ERT access is often limited due to high costs, inconsistent global supply chains, and a restricted healthcare infrastructure, such as exclusion from the formulary of major government hospitals.⁽²⁰⁾ These issues are apparent in SA, as long-term affordability and OD supply remain challenging despite centralised procurement systems.⁽²⁷⁾ Notably, hematopoietic stem cell transplantation (HSCT) offers limited benefit for skeletal and cardiac symptoms of MPS-VI, with outcomes depending on age at transplantation and donor match.⁽²⁰⁾ Gene therapy is still in the experimental phase; nevertheless, early preclinical research on adeno-associated virus (AAV) -mediated *ARSB* delivery appears promising for reducing glycosaminoglycan buildup and increasing enzyme activity.⁽²⁰⁾ Hence, present treatments mainly provide support, emphasising the urgent need for sustainable and accessible therapeutic options.

In SA, recent national efforts have suggested various strategies, emphasising the need for improved RD care. In King Fahad Medical City (KFMC), one of the country's largest tertiary medical centres, Galsulfase procurement is subject to patient-specific approval under the MOH. This approval process can delay treatment and potentially impact clinical outcomes.

Altogether, these challenges contribute to the unique genetic profile of SA, characterised by high rates of CM,^(28, 29) which significantly contributes to the increase in MPS-VI incidence.^(17, 30, 31) Additionally, despite growing national awareness of RDs, published data detailing the real-world experiences of patients with MPS-VI and their family members remain lacking, particularly concerning diagnostic delays, treatment access barriers, and long-term follow-up within the SA healthcare system.

Hence, this study aimed to explore the diagnostic pathways, treatment experiences, and follow-up care of patients with MPS-VI and their parents at KFMC in SA to identify obstacles in their clinical journey. Additionally, patient experiences at KFMC were comprehensively assessed, highlighting gaps in access, recommending system-level improvements, and supporting future policies and clinical practices to improve MPS-VI care.

Methods

A sequential explanatory mixed-methods design was used to explore the clinical journeys and lived experiences of patients with MPS-VI at KFMC. Initially, the clinical and treatment data were retrospectively extracted from Electronic Medical Records (EMRs) and analysed to quantify patterns of diagnosis, referral, and ERT outcomes.

Following this, a descriptive, exploratory, and qualitative analysis was conducted, involving semi-structured interviews with family members of patients with MPS VI, conducted in person or by phone, depending on the participant's preference. As a result, personal and contextual factors underlying the observed quantitative patterns were examined.

Through this sequential explanatory mixed-methods design, the measurable trends were identified, and then their underlying causes were interpreted using stakeholder narratives. This enabled a more comprehensive, context-sensitive understanding of the patient experience.

Participant Eligibility and Recruitment

A purposive sampling strategy was used to enrol participants in this study. Eligible participants included patients with MPS-VI who actively received ERT with Galsulfase at KPMC, along with their family members. Patients with coexisting conditions that could affect their prognosis or response to treatment, and those who were not currently receiving Galsulfase, were excluded from the study. Family members of enrolled patients were approached individually, given a clear explanation of the study's purpose and procedures and invited to participate.

Data Collection Instruments

The quantitative data were collected from EMRs using customised Excel-based templates **[Supplementary Material (1): Electronic Medical Records (EMR) Data Collection Template]**. Data were collected by the researchers. In the templates, essential clinical and demographic variables were recorded, as follows: patient age, sex, height, weight, clinical symptoms, number of specialist consultations before diagnosis, date of genetic testing, and timelines for ERT initiation. Disease progression and treatment effectiveness were assessed using clinical parameters, including 6-minute walk test (6MWT) performance, uGAG levels, and anthropometric measures (height and weight), documented at baseline and during follow-up post-ERT.⁽³²⁾

The variables were selected in accordance with established clinical practice guidelines and an international expert consensus on monitoring patients with MPS-VI undergoing ERT.⁽⁶⁾ Specifically, the study tracked functional endurance, biochemical markers of storage burden, and physical growth metrics as critical indicators of therapeutic response and long-term clinical outcomes.⁽²⁰⁾

The semi-structured interviews were conducted using a topic guide developed by clinical experts in metabolic disorders and by qualitative methodologists. The guide was designed to explore key areas, including patient and parent demographics, diagnostic experience, treatment pathways, challenges encountered, and proposed solutions. Following the design of the initial version of the topic guide, questions were based on existing literature^(4, 20, 33) and study objectives; the initial version was reviewed by HAA to ensure face and content validity. Next, the guide was piloted in two mock interviews, including one with a methodological expert and another with a family member of a child with RD. This allowed for the refinement of language, structure, and question clarity. Following the feedback, minor adjustments were made to improve clarity, flow and relevance. The final guide was consistently approved by (HAA and AM) and used across all interviews to ensure coherence and alignment with the aims of the study

[Supplementary Material (2): Semi-structured Interview Guideline, Patients with MPS VI (or Their Carers)]. Both pilot interviews and their analyses were excluded from the study.

To structure and contextualise patient pathways, the diagnostic and treatment trajectories of patients with MPS-VI were mapped using EMR-extracted data and triangulated using family members' interviews. This mapping exercise captured the sequence of events from symptom recognition to ERT initiation. Notably, five key steps were identified in the pathway: (1) symptom onset, referring to early signs, including coarse facial features, delayed walking, or growth concerns noticed by parents; (2) initial medical consultation, indicating the first healthcare encounter where concerns were raised; (3) referral to a specialist, marking the transition to genetic or metabolic care; (4) diagnosis, defined as the point of confirmed MPS-VI identification; and (5) ERT initiation, representing the start of disease-specific treatment. This framework enables cross-case comparisons and the identification of delays or bottlenecks in the care pathway.

Interview appointments were scheduled to align with the patient's treatment plan by contacting the day care unit at KFMC, a unit designed to provide specialised care for patients undergoing same-day surgical procedures or other treatments that do not require an overnight stay. This was carried out to confirm their ERT appointments. On the day of the interview, family members were approached in person, provided with the study information sheet **[Supplementary Material (3): Patient Information Sheet]**, and invited to participate. All interviews were recorded using either a digital recorder or through an online meeting platform.

Data Analyses

For quantitative analysis, descriptive statistics were employed to analyse patient demographics, clinical indicators, and treatment-related timelines. For continuous variables, such as height and 6MWT distance, changes from the baseline to the last follow-up visit were reported as mean differences to show treatment-related improvements. Furthermore, frequencies and percentages were summarised for categorical variables, including diagnostic delays and barriers to access ERT. All analyses were performed manually using Microsoft Excel. Owing to the small sample size, clinically meaningful patterns were identified rather than statistical significance being tested.

For the qualitative analysis, all audio-recorded interviews were transcribed verbatim, and the data were combined with manually written field notes. The transcripts were uploaded to NVivo® (version 15) for organisation and coding. Additionally, thematic analysis was applied following Braun and Clarke's six-phase framework: (1) data familiarisation, (2) initial code generation, (3) theme searching, (4) reviewing themes, (5) defining and naming themes, and (6) report production.⁽³⁴⁾ Two researchers (GA and HAA) independently coded transcripts and then met to discuss the generated themes and subthemes to ensure consistency and to discuss any discrepancies to reach consensus. Thematic analysis was inductive and aligned with the study's objectives to ensure analytical rigour and transparency.

Ethical Considerations

Ethical approval

for this study was obtained from the Institutional Review Board (IRB) of PNU, Riyadh, SA (IRB Log Number: 23–0447, approval date: May 18, 2023) and from the IRB of KFMC, Riyadh, SA (IRB Number: 24–532, approval date: September 25, 2024). All participants provided written informed consent before participation in the study and interview **[Supplementary Material (4): Patients & their Family Consent Form]**. Confidentiality and anonymity were rigorously maintained throughout the study, in line with institutional ethical standards.

Results

Patients and their Family Members' Demographic and Characteristics Profiles

In total, nine patients with MPS-VI who were undergoing active Galsulfase treatment were included in this study. The group included three females (33.3%) and six males (66.7%) (age range: 5–16 years; mean $\pm$ standard deviation: 10.1 ± 3.3 years). Most of the patients lived in the central region of SA, and Riyadh ($n = 3$) and Al-Kharj ($n = 2$) were the most common locations. Additionally, three patients came from Hail and one from Al-Qassim.

Of the seven patients whose family members (parents and siblings) participated in the qualitative interviews, the following four were interviewed in person: two with mothers (one caring for two patients with MPS-VI) and one with a sister. The other three interviews were conducted by phone, including two with mothers and one with a father, depending on the participant's preference and availability. The remaining eligible family (with two siblings) declined to participate, despite multiple follow-up calls.

The educational backgrounds of these patients varied as follows: two children were of school age but had not yet enrolled in school due to parental concerns about their physical readiness for a traditional classroom setting. Additionally, instead of a conventional school curriculum, one child was enrolled at the Centre for Special Education and Rehabilitation in Al-Kharj, which offers individualised educational and developmental services for children with physical and learning challenges. Lastly, four patients attended private schools at different grade levels: two in primary school (second and third grades), one in intermediate school, and one in secondary school.

Parental consanguinity was documented in all six families (nine patients) included in the study. Most cases involved first-cousin marriages ($n = 4$), whereas others involved relationships with more distant cousins. These findings strongly correlated consanguinity and genetically interconnected family structure. Notably, a confirmed family history of MPS-VI was observed in two families, each with two siblings diagnosed with the condition. These characteristics are summarised in Table 1.

Table 1
Patient Demographic and Socio-Familial Characteristics

Variable	n = 9	%	Additional Details
Gender			
Male	6	66.7%	
Female	3	33.3%	
Age (years)	-	-	Mean $\pm$ SD: 10.1 $\pm$ 3.3; Range: 5–16
Region of Residence			
Riyadh	3	33.3%	
Al-Kharj	2	22.2%	
Hail	3	33.3%	
Al-Qassim	1	11.1%	
Parental Interview Participation			
Participated	7	77.8%	4 in-person; 3 by phone
Declined or Unavailable	2	22.2%	One family with two siblings
Educational Status			
Not enrolled	2	22.2%	Due to concerns about readiness
Center for Special Education	1	11.1%	Al-Kharj; not a standard school
Enrolled in Private School	4	44.4%	2 primary (2nd & 3rd), 1 intermediate, 1 secondary
Parental Consanguinity	7 families	100%	5 first cousins; 2 distant cousins
Family History of MPS-VI	2 families	-	Each with two affected siblings
<i>Mucopolysaccharidosis VI (MPS-VI); Standard Deviation (SD).</i>			

Age of the Patient at Diagnosis and ERT Initiation

In this study, the enrolled patients were generally diagnosed at a young age. Among those with available data, the median age at diagnosis was approximately 2.0 years (range: 1.1–7.2 years). Notably, one patient was diagnosed significantly later than the remaining patients at 7 years and 2 months. In three cases (Pt. 2, Pt. 7, and Pt. 8), the age at diagnosis was not available in the EMR but was obtained

through semi-structured parent interviews and included in the analysis to ensure data completeness and accuracy Table 2.

Table 2

The Journey of Patients with Mucopolysaccharidosis VI (MPS VI): Insights from EMRs and Family Interviews

Patient (ID)	Data Source	Symptom Onset Date	1st Date the Patient is seen by the physician	Referral Date to a Specialist, genetic or metabolic physician	Diagnosis Date	Initiation of ERT Date
Pt. 1	EMR (DD/MM/YY)			22/07/2019* King Khaled Hospital (Hail) into Metabolic-Ped at KFMC		23/01/2020
	SI (yr)	1.0 yr (facial changes)	1.0 yr (hospital visit in Hail)	2.0 yrs (referral to Riyadh, delayed to ~ 3)	3.0 yrs	3.5 yrs
Pt. 2	EMR			27/09/2017* King Khalid Hospital & Prince Sultan Centre for Health Services (Al-Kharj) into the Spine Deformity clinic at KFMC		18/09/2018
	SI	1.8 yrs	1.6 yrs (late walking concern)	5.0 yrs (after prolonged delays)	5.0 yrs	5.0 yrs
Pt. 3	EMR			24/04/2022		24/07/2022
	SI	Not specified	1.7 yrs (screening due to sibling)	1.7 yrs (direct metabolic consult)	1.7 yrs	1.9 yrs
Pt. 4	EMR			14/03/2019 * Security Forces Hospital (Al-Riyadh) into Metabolic-Ped at KFMC		04/02/2021
Electronic Medical Records (EMR); Semi-Structured Interview (SI); Enzyme Replacement Therapy (ERT); King Fahad Medical City (KFMC); Years (yrs); *Approved Referral date.						

Patient (ID)	Data Source	Symptom Onset Date	1st Date the Patient is seen by the physician	Referral Date to a Specialist, genetic or metabolic physician	Diagnosis Date	Initiation of ERT Date
	SI	1.0 year (growth features)	1.0 year (clinic visit for fever)	1.5 yrs (genetic workup begun)	2.0 yrs	2.5 yrs
Pt. 5	EMR			05/11/2019 * King Khaled Hospital (Hail) into Metabolic-Ped at KFMC		23/03/2021
	SI					
Pt. 6	EMR			04/07/2022 * Maternity and Children's Hospital (Hail) into Metabolic-Ped at KFMC		26/02/2023
	SI					
Pt. 7	EMR			N/R		06/02/2012
	SI	1.0 year (coarse features)	1.5–2.0 yrs (pediatric consult)	2.0 yrs (referred to KFMC)	2.0 yrs	2.8 yrs
Pt. 8	EMR			28/01/2018* Maternity & Children Hospital (Qassim) into Metabolic-Ped at KFMC		04/04/2019
	SI	2.0 yrs	2.0 yrs	3.0 yrs	3.0 yrs	3.3 yrs
Pt. 9	EMR			22/11/2011		24/02/2015
	SI	1.0 yr	1.0 yr (multiple physicians consulted)	4.0 yrs (eventual specialist referral)	4.3 yrs	4.5 yrs
Electronic Medical Records (EMR); Semi-Structured Interview (SI); Enzyme Replacement Therapy (ERT); King Fahad Medical City (KFMC); Years (yrs); *Approved Referral date.						

The median age of the patients initiated on ERT was 3.3 years. For these patients, the time between diagnosis and initiation of ERT ranged from immediately to approximately 2 years. Notably, four patients (Pt. 1, Pt. 2, Pt. 3, and Pt. 7) were initiated on ERT immediately or within a short period (0–1 month) post-diagnosis. A further four patients (Pt. 4, Pt. 6, Pt. 8, and Pt. 9) were initiated on ERT within 2–11 months of diagnosis. One patient (Pt. 5) experienced a delay of a year or more before initiating ERT after diagnosis.

Journey to ERT: Integrating EMR Data with Experience of the Parents

In all nine cases, the results showed early clinical features, including coarse facial features, growth delay, and gait disturbances, typically observed within the first two years of life. Although initial medical consultations usually occurred around 1–2 years of age, referral patterns varied markedly. In six of the nine cases, the diagnostic workup was initiated outside the KFMC, followed by a formal referral to the general paediatrics department, which then directed the cases to the metabolic team.

For example, Pt. 1 was first seen at King Khaled Hospital in Hail before being referred to the metabolic-pediatric unit at KFMC. Pt. 2 started care in Al-Kharj; however, owing to administrative delays, referrals to KFMC were delayed until 5 years of age, despite symptoms beginning at around 2.5 years old. These patients (Pts. 5, Pt. 6, and Pt. 8) followed similar paths and were initially evaluated at external hospitals before being referred to KFMC for specialist care. While Pt. 4 began evaluating at the Security Forces Hospital, Riyadh, the family was referred to the KFMC for treatment after a genetic diagnosis.

In contrast, three patients (Pts. 3, Pt. 7, and Pt. 9) completed their diagnostic and treatment journey at the KFMC. Notably, a patient (Pt. 3) was identified early based on the sibling's screening results and was promptly referred to the KFMC metabolic clinic. Moreover, Pt. 9 had ongoing follow-up at KFMC since birth, whereas Pt. 7 lacked referral data in Table 3, and the maternal parent reported that the patient was referred to KFMC specialists at around age 2. These cases show the typical institutional pathway from general to metabolic paediatrics within the KFMC.

Table 3
Age at Diagnosis versus Age at Initiation of ERT

Patient (ID)	Gender	Data Source	Age at Diagnosis (yrs)	Age at ERT Initiation (yrs)	Duration Difference months (yrs)
Pt. 1	Female	EMR	2 yrs 1 m	N/R	-
		SI	2 yrs	2 yrs	0
Pt. 2	Female	EMR	N/R	5 yrs 9 ms	-
		SI	5 yrs Referral was recommended at ~ 2½ y but delayed until 5 y due to paperwork issues	5 yrs	0
Pt. 3	Male	EMR	2 yrs	2 yrs	0
		SI	1 year 8 m	2 yrs (≈ 1 year 9 m)	1 m
Pt. 4	Male	EMR	1 year 5 m	2 yrs 4 ms	11 ms (≈1)
		SI	1 year 6 m 6-month wait for genetic test results, multiple evaluations before final diagnosis	2 yrs 6 ms	≈ 1 yr
Pt. 5	Male	EMR	1 year 1 m	3 yrs 3 ms	27 ms (≈ 2 yrs)
		SI			
Pt. 6	Female	EMR	7 yrs 2 ms	7 yrs 8 ms	7 ms
		SI			
Pt. 7	Male	EMR	N/R	2 yrs 8 ms	-
		SI	2 yrs	2 yrs	0
Pt. 8	Male	EMR	N/R	3 yrs 3 ms	-
		SI	1 yr	1 year 2 ms	2 ms
Pt. 9	Male	EMR	3 yrs 8 ms	4 yrs 5 ms	8 ms
		SI	3 yrs	3 yrs 1–2 m	1–2 ms

No recorded value (N/R); Electronic Medical Records (EMR); Semi-Structured Interview (SI); Enzyme Replacement Therapy (ERT); months (m); Years (yrs).

Patient (ID)	Gender	Data Source	Age at Diagnosis (yrs)	Age at ERT Initiation (yrs)	Duration Difference months (yrs)
			after long diagnostic odyssey	treatment delayed ~ 1 m for medication import	
No recorded value (N/R); Electronic Medical Records (EMR); Semi-Structured Interview (SI); Enzyme Replacement Therapy (ERT); months (m); Years (yrs).					

The results of the quantitative analysis showed that the average periods from symptom onset to confirmed diagnosis and from diagnosis to ERT initiation were approximately 24 months and 19 weeks, respectively. These results highlighted two key bottlenecks in the MPS-VI care process: a prolonged diagnostic period of nearly 2 years and a treatment delay of > 4 months post-diagnosis.

Overall, these findings revealed a significant variability in referral efficiency and treatment timelines. Furthermore, they emphasised how regional healthcare access, referral coordination, and institutional infrastructure affect timely diagnosis and treatment initiation. To address these challenges, targeted interventions for early recognition in peripheral hospitals, streamlined referral processes, and faster treatment approval need to be employed to ultimately enhance patient outcomes.

These case-level patterns reveal a broader systemic reality. Notably, patients with less access to major urban centres often face fragmented referral pathways and prolonged delays, which can be attributed to institutional bottlenecks and regional disparities in healthcare access. Tackling these issues requires earlier recognition and referral, as well as improved interfacility coordination and logistical streamlining.

In addition to mapping referral patterns and diagnostic delays, evaluating clinical outcomes is essential to understanding the impact of ERT. The following sections present long-term data on physical growth and functional endurance, as demonstrated through changes in anthropometric measures and 6MWT performance. These findings provide valuable insights into the therapeutic benefits of ERT in children with MPS-VI.

Clinical Outcomes of ERT: Long-Term Changes in Growth and Physical Endurance in MPS-VI Patients

- **Anthropometric Changes Before and After ERT.**

Herein, all patients showed considerable improvements in height and weight measurements during ERT (Table 4 **and** Fig. 1). Notably, the average height increased by approximately 17.2 cm, with gains ranging from 1.5 cm in Pt. 6 to 35 cm in Pt. 8. The most significant increases in height were observed in patients with longer ERT durations. Patients (Pt. 7 and Pt. 8), who received ERT for > 13 and 6 years, respectively, presented with the highest gains (34–35 cm).

Table 4
Anthropometric Changes Between First and Last Visits

Patient (ID)	Height (cm)			Weight (kg)			Over (yrs)
	Before ERT	Last Visit after ERT	Difference	Before ERT	Last Visit after ERT	Difference	
Pt. 1	91	98.5	7.5	13.1	16.55	3.5	3 yrs, 5 months
Pt. 2	86	98	12	11.7	17	5.3	6 yrs, 9 months
Pt. 3	79	94	15	9.1	12.5	3.4	2 yrs, 11 months
Pt. 4	88	111	23	11.2	21.5	10.3	6 yrs, 2 months
Pt. 5	85	100	15	10.95	17.45	6.5	3 yrs, 8 months
Pt. 6	105	106.5	1.5	16.6	19.3	2.7	1 year, 9 months
Pt. 7	99	133	34	14.2	29.6	15.4	13 yrs, 4 months
Pt. 8	89	124	35	14.1	20	5.9	6 yrs, 2 months
Pt. 9	89.5	101	11.5	14.2	22	7.8	10 yrs, 3 months
<i>Enzyme Replacement Therapy (ERT); Years (yrs).</i>							

The trend in weight gain was similar, with an average increase of 6.76 kg. Similar to height measurements, the highest weight gain was observed in Pt. 7, who gained 15.4 kg, whereas the smallest increase occurred in Pt. 6, who gained 2.7 kg. Notably, Pt. 6 had the shortest treatment duration of 1.75 years. These results clearly demonstrate that improvements in height and weight tended to align with the duration of ERT exposure.

Although no inferential statistics were used because of the small sample size, the descriptive trends (Fig. 1) suggested a dose–response relationship. Longer ERT durations positively correlated with greater anthropometric improvements, especially when initiated earlier in childhood. Overall, these findings align with existing literature, reinforcing the benefits of early and ongoing ERT in supporting growth in patients with MPS-VI. They also highlight the importance of a timely diagnosis and continuous access to treatment to optimise long-term physical development.

These results may be attributed to a combination of age-related physiological development and the therapeutic effects of long-term ERT. These findings are consistent with the existing literature, which

suggests that early initiation and consistent use of ERT can improve growth outcomes in patients with MPS-VI.

• Performance of Six-Minute Walk Test (6MWT) Pre- and Post-ERT

In total, nine patients with MPS-VI at the KFMC were evaluated for functional endurance using the 6MWT before and after ERT. Notably, baseline (pre-ERT) 6MWT distances were available for five patients (range: 108–343 m), indicating heterogeneous pretreatment mobility. Following ERT, four of these five patients showed considerable improvement in 6MWT performance, with distances walked increasing by approximately 67–87 m compared with that at baseline after 2–5 years of ERT. The walking distance of other patients remained essentially unchanged (343.2 m pre-ERT versus 335 m post-ERT after 1.8 years). The magnitude of improvement observed in the present cohort (mean increase of approximately 75 m among responders) was comparable to the therapeutic benefits reported in clinical trials. Notably, the EMA reported a mean increase of 92 m in the 6MWT at 24 weeks post-ERT. ⁽³⁵⁾

In the present study, individual patient responses to ERT varied considerably, and no clear relationship was observed between treatment duration and the extent of 6MWT improvement. Patients treated for 3–5 years achieved distance gains similar to those treated for shorter periods (approximately 2–3 years). Notably, a patient with high baseline endurance (343 m) showed a slight decline in 6MWT distance despite 1.75 years of therapy, suggesting a possible ceiling effect or test variability. All patients completed the 6MWT after ERT initiation; however, some continued to exhibit exertional limitations. For example, one patient developed bradypnea and slowed down after approximately 132 m, and another patient required brief rest pauses (8–11 s each) during the test because of fatigue and shortness of breath, even after years of ERT.

In the remaining four cases, no pre-ERT 6MWT was documented, which precluded a direct comparison of pre- and post-therapy performance for those individuals. Notably, the post-ERT distances for these patients ranged from 208 to 320 m, indicating moderate functional capacity, although their baseline status remains unknown. Additionally, uGAG levels were not measured; therefore, the biochemical response to ERT could not be assessed alongside the functional outcomes. Despite these limitations, the overall trend in this study's results indicates that long-term ERT generally stabilises or improves ambulatory capacity in patients with MPS-VI. Most patients showed meaningful gains in endurance, although residual exercise intolerance (manifested as easy fatigability and exertional dyspnoea) persisted in some cases Table 5.

Table 5
Six-Minute Walk Test Performance (Pre- and Post-ERT)

Patient (ID)	6MWT pre-ERT (m)	6MWT post-ERT (m)	Duration (Yrs, Months)
Pt. 1	199.5 m, 3 rests, patient tolerated the test, no fatigue.	266.3 m, no rest interval, patient completed the test without stopping or any complications.	2 Yrs, 11 months
Pt. 2	Not Done	320 m, without breaks or falls. No orthosis or shoes. The patient's walking speed differed at each time and started to get fatigued in the last minute.	-
Pt. 3	Not Done	300 m, without breaks or falls. No orthosis or shoes. The patient's walking speed differed at each time point and began to fatigue in the last minute.	-
Pt. 4	108 m. Had 1 break without use of any assistive devices nor orthoses.	195 m, normal speed. Patient must rest for 20 seconds without signs of shortness of breath.	5 Yrs
Pt. 5	160 m, Patient stepped for a few seconds to catch the breath between labs. Patient was able to complete around 16 laps. At 2:50 minutes, patient starts to get tired but continues to walk independently. At 4:30 minutes, patient starts to cry but continues walking. Patient completed all the 6 minutes.	231 m in 6 minutes. Patient walked for 180 m. in 4 minutes then rested for 1.5 minutes then walked for 51 meter in 2 minutes.	4 Yrs, 10 months
Pt. 6	343.2 m and no rest in between	335 m with no rest, patient started bradypnea after 132 m. and reduced her speed at 180 m.	1 Yrs, 9 months
Pt. 7	Not Done	250 m without any falls	-
Pt. 8	285 m; take a rest for 5 minutes	363 m without breaks and change breath.	3 Yrs, 4 months
Pt. 9	Not Done	208.5 m. Starts to have shortness of breath at minutes of 4:50. Become more significant at 4:14. Rest for 8 seconds at minutes of 2:52. 11 seconds rest at the minutes of 2:14. Patient sat at the last 17 seconds then continues walking for 3.5 m.	-
Not done because the patient did show up. Six-Minute Walk Test (6MWT); Enzyme Replacement Therapy (ERT); Years (yrs).			

Qualitative findings

In the present study, four main themes and eight subthemes were identified through semi-structured interviews as follows: (1) Diagnostic and Care Provision Inequities, (2) Treatment Pathways and Continuity of Therapy, (3) Logistical Burdens and Care Coordination Gaps, and (4) Psychosocial and Emotional Strain. Each theme included subthemes and illustrative quotations, offering insights into patients' and their families' experiences.

Theme 1: Diagnostic and Care Provision Inequities

This theme explores the unequal access to timely diagnosis and specialist care for children with MPS-VI. Families described long and uncertain diagnostic journeys marked by multiple misdiagnoses, conflicting medical opinions, and delayed referrals. Limited regional expertise, fragmented care pathways, and associated educational barriers compounded these challenges, leading some families to travel long distances or seek treatment abroad. These accounts highlight the need for earlier detection, equitable distribution of specialist services, and coordinated health and education support.

Subtheme 1.1: Delayed Diagnosis and Uncertainty

For most families, the diagnostic process begins with subtle, unclear signs that are often mistaken for common childhood illnesses. This led to multiple misdiagnoses and a delayed diagnosis of MPS-VI. Families described this period as emotionally complex, full of confusion, and lacking clear guidance from their healthcare providers.

For example, one parent recounted, “We had trouble getting the correct diagnosis and were given about five different diagnoses (water on the head, blood disease, liver disease, etc.)” for Pt. 9. Another family shared, “The main difficulty was the delay in referral to Riyadh and conflicting opinions from physicians initially” for Pt. 1.

However, the patients were not isolated. Many parents reported receiving contradictory diagnoses across multiple visits to different physicians, often conveying conflicting information that increased their frustration and anxiety. For instance, a parent described the emotional toll as follows: “What hurts me most is... the delay in diagnosis and the lack of clarity about the condition at first was stressful.” Similarly, another stated, “We kept getting different answers each time we visited a new physician” for Pt. 2.

Owing to diagnostic uncertainty, many parents adopted an approach of conducting independent research, seeking second opinions, and requesting additional tests. For example, the mother of Pt. 7 shared, “I read online about his symptoms and pushed for a genetic test,” highlighting the importance of parent advocacy in expediting diagnosis. Overall, these experiences reveal significant gaps in local clinical awareness and emphasise the need for earlier detection of RDs, such as MPS-VI.

Subtheme 1.2: Scarcity of Rare Disease Expertise and Fragmented Referral Pathways

This subtheme highlights the experiences of families with limited access to MPS-VI specialists outside major cities, resulting in delayed diagnoses and increased reliance on centralised facilities in Riyadh, SA. Most participants described the healthcare system as fragmented, with local providers often unfamiliar with the conditions, necessitating referrals to tertiary hospitals for proper assessment and treatment. A parent of Pt. 1 expressed a common sentiment, “I wish there were specialised physicians in regions outside Riyadh to enable early diagnosis.”

Many families highlighted the scarcity of trained genetic specialists from their respective regions. Pt. 8’s father said, “We have one genetic clinic in Al Qassim but no MPS-VI specialist,” while the maternal parent of Pt. 2 added, “In our area, no one even knows about this condition.” These comments point to a significant geographic disparity in RD expertise, resulting not only in delayed diagnosis but also in families having to travel long distances for care. The parent of Pt. 8 also proposed establishing a dedicated genetic clinic in Qassim to address these gaps.

These infrastructural problems extend beyond the healthcare system and affect the educational sector. Finding suitable schools for their children was challenging for parents, and they often faced stigma or misconceptions about the cognitive effects of MPS-VI. One mother explained that the child was denied entry into mainstream education because of the assumption of intellectual disability, and the child’s intelligence quotient was tested to prove their abilities. Pt. 8’s father mentioned, “No government school in Al Qassim suits him,” while Pt. 7’s mother stated, “We couldn’t find a school that could accommodate his needs.”

The lack of specialised local services often leads to lengthy, complex referral processes. The mother of Pt. 2 emphasised the importance of early intervention and regional expertise, stating that “Specialised physicians and early diagnosis in areas outside Riyadh ” are needed.” Some families facing long waiting times in the public healthcare sector chose to pursue follow-up care abroad. One of the parents stated, “We have insurance and conduct follow-ups abroad... [to] bypass long public wait times.”

These experiences collectively highlight the urgent need for decentralised RD services, expansion of regional genetic screening and counselling, and promotion of collaboration across sectors, such as health and education. Improving access to multidisciplinary experts, including trained educators, could significantly reduce diagnostic delays, travel burdens, and long-term outcomes in children with MPS-VI. This approach can also help reduce stigma, enable quicker diagnosis, and support greater social inclusion.

Theme 2: Treatment Pathways and Continuity of Therapy

This theme examines the experiences of starting, maintaining, and occasionally interrupting ERT, a lifelong weekly treatment essential for managing MPS-VI. While families generally demonstrated strong commitment to treatment, systemic inefficiencies, supply chain issues, and inconsistent access to supportive services disrupted care. These findings underscore the importance of reliable medication

availability, accurate dosing, and efficient coordination between pharmacies and infusion units to maintain continuous therapy and build trust in the healthcare system.

Subtheme 2.1: Initiation and Maintenance of ERT

After diagnosis, families reported various challenges in starting and maintaining ERT. They received a thorough education regarding ERT before treatment. In all cases, the families signified the importance of the treatment as a part of their care. Patients were provided with detailed information regarding ERT before initiating treatment. Pt. 7's mother explained, "He should receive weekly treatment... It won't cure him, but it will help maintain his current state," reflecting a broader understanding among families that ERT was palliative rather than curative.

Once initiated, therapy was usually maintained consistently, and most parents report few adverse effects. For example, Pt. 2's mother stated, "No symptoms appeared except for a very minor one the first time. It has now been seven years... and I haven't experienced any other side effects." Similarly, the sibling of Pt. 9 also described a stable routine, stating that the child "was taken regularly... even given while travelling," despite initial allergic reactions and adjusted infusion times.

Despite this consistency, medication-related issues have emerged as significant barriers to effective care. Many families experienced logistical and systemic problems at hospital pharmacies, including the unavailability of ERT, delays in medicine preparation at the day-care unit, and dosing errors. For example, the sibling of Pt. 9 recounted, "We were forced to go home without taking the medication... happened about three times," due to the drug being unavailable at the hospital. Pt. 7's mother also reported concerns about dosing: "They were giving him a lower dose than he was supposed to take," which raised questions about quality control and protocol adherence in medication management.

Most families reported few side effects and consistent dosing once the treatment was initiated. For example, Pt. 2's mother noted for the first time, "no symptoms appeared except for a very minor one the first time. It has now been seven years... and I haven't had any other side effects." Additionally, the sibling of Pt. 9 mentioned allergic reactions and changes to infusion time but maintained the overall consistency; the child "was taken regularly... even given while travelling."

These challenges expose structural gaps in the hospital systems that undermine therapeutic adherence and outcomes even when parents are prepared and compliant. Furthermore, they highlight the importance of timely access to medications, accurate dosing, and efficient coordination between pharmacies and infusion units for effective ERT delivery functioning. Addressing these issues is crucial not only for achieving better individual patient outcomes but also for building trust in the healthcare system's ability to effectively manage RDs.

Subtheme 2.2: Treatment Interruptions

Although all patients eventually began a regular ERT regimen, various logistical, clinical, and systemic challenges often disrupted treatment. Common obstacles included illness (particularly febrile episodes),

travel commitments, scheduling conflicts in the day care unit, and broader disruptions such as the coronavirus disease-2019 pandemic. For example, the therapy of Pt. 1 was “paused during the COVID-19 pandemic,” whereas in the case of Pt. 7, the care team initially suggested stopping treatment; however, his mother resisted and filed multiple complaints, ultimately convincing the team to resume therapy under her supervision.

Reportedly, inefficiencies in the pharmacy and supply chains have led to such interruptions in multiple cases, including delays in medication preparation and poor communication about drug availability. Such activities further increased parental stress and potentially reduced treatment effectiveness. The sibling of Pt. 9 explained, “Sometimes they say the medication is out of stock, and we have to come again next week,” whereas Pt. 7’s mother recalled, “The nurse said they were preparing it, but we waited four hours before it was ready.” These observations highlight the need for more efficient pharmacy coordination and clear communication protocols to prevent avoidable disruptions in care.

Some families even considered approaching home healthcare services to reduce treatment delays; however, their experiences varied. The mother of pt. 3 reported two “very bad” experiences with untrained home infusion staff, which further exacerbated complications such as cramping and vomiting. The parent said, “She gave him the dose all at once instead of a drip... he cramped and vomited,” which caused the family to refuse further home-based treatment and demand hospital-administered infusions. Meanwhile, Pt. 8’s father presented a more promising option with a private healthcare provider in Al Qassim, who offered to deliver therapy at home if there was sufficient space. However, many families in Riyadh who were interested in home care turned away due to geographic restrictions, further exposing disparities in access to services.

Despite these obstacles, families generally accepted that ERT is a lifelong therapy for symptom management rather than a cure. A doctor explained to the family of Pt. 4, “Treatment relieves symptoms only... [it] must be continuous for life.” For instance, the effects of missed doses varied among patients. For example, the Pt. 2’s mother reported a return of leg pain during a short interruption, which went away once treatment resumed: “After resuming treatment, the pain went away.” In contrast, the mother of Pt. 4 observed little clinical change during a 1-month break due to travel. These different experiences highlight the importance of ensuring consistent treatment and the need for flexibility to accommodate real-life situations. Collectively, these observations highlight the delicate balance between ongoing therapy and the practical challenges many families face, underscoring the need for a reliable supply chain, equitable access to home infusion services, and alternative delivery options to ensure ongoing treatment.

Theme 3: Logistical Burdens and Care Coordination Gaps

This theme highlights the practical and organisational challenges of ongoing care for MPS-VI. Families, particularly those living far from Riyadh, faced significant strain from frequent travel, accommodation costs, and time away from work. Inefficient scheduling and fragmented coordination between specialities added to these burdens, especially for households with multiple affected children. Improving

local service availability, providing logistical support, and adopting multidisciplinary scheduling models could help reduce these pressures.

Subtheme 3.1: Travel and Accommodation Strain

Families living outside Riyadh, including those in Hail, Qassim, and Al-Kharj, reported significant challenges with travel and accommodation when accessing care at the KFMC. Regular weekly trips for ERT placed a heavy burden on families, straining their time, finances, and overall well-being. The parent of Pt. 1 described, “It was harder when we had to travel to Riyadh every week,” adding that they had to “rent an apartment at our own expense.” Work-related issues further exacerbated these logistical challenges. The father of Pt. 8, a soldier in Qassim, explained, “I had to ask for leave from work every time we had an appointment,” while the parent of Pt. 3 noted, “His salary was deducted if he took more than four hours off.”

Although hospital accommodations were sometimes offered, their usefulness was limited. For example, the family of Pt. 3 received an apartment that was not practical because of its distance: “Yes, they provide accommodation, but it is too far from the hospital, so we cannot [use it]. We usually come in our car.” In another instance, the family said that they had to sleep in their cars because there were no other options. The father of Pt. 8 faced a similar problem when appointments lasted several days, stating, “I have to rent an apartment... I never contacted anyone about accommodation support,” indicating a general lack of awareness of available support.

These experiences highlight the substantial indirect costs families face, including transportation, lodging, and lost work. The absence of organised logistical support further exacerbates their financial and emotional burdens. Enhancing local access to services or offering accommodation subsidies, along with clearer information about support entitlements, may reduce these burdens.

Subtheme 3.2: Inefficient Care Coordination

Families expressed significant concern about fragmented scheduling and inefficient coordination among specialities. For those with multiple affected children, uncoordinated appointments posed logistical challenges. For example, the parent of Pt. 3 clearly explained that “Appointments are often separate... I get nervous with both crying,” emphasising the need for synchronised scheduling. Although the parent valued the clinical staff, “physicians were very cooperative,” the lack of a formal coordination system remained challenging.

Similarly, the Pt. 8’s father also reflected on the strain caused by poorly coordinated appointments, stating, “Some appointments will be on consecutive days. So, I have to rent an apartment... when we tried to speak with the physician, there was barely time because he was busy.” The cumulative stress of managing unorganised schedules, frequent travel, and multiple consultations without central oversight significantly worsened the parents' fatigue.

These accounts highlight systemic gaps in RD care coordination. Families are often left to manage complex appointments without the dedicated support of a case manager or streamlined booking system. To address this, implementing multidisciplinary scheduling blocks or quarterly consolidated visits, such as the triple-clinic model referenced by one of the families, may be the best practice for reducing the logistical burden on parents.

Theme 4: Psychosocial and Emotional Strain

This theme addresses the emotional and social challenges faced by families living with MPS-VI. Parents described the distress of diagnosis, the ongoing strain of weekly treatments, and the impact of stigma and misconceptions. While some drew strength from personal resilience or faith, most lacked access to formal psychological support services. Addressing these needs through integrated mental health care and targeted psychosocial interventions could improve overall family well-being.

Subtheme 4.1: Emotional Strain, Stigma, and Coping Mechanisms

The parents universally described the initial diagnosis of MPS-VI as emotionally devastating, with many comparing moments to emotional breakdowns. For instance, the Pt. 4's mother recalled, "I felt like the world was turning black in front of my eyes." She was "shocked and scared" by the diagnosis and expressed grief seeing the child growing more "resentful" and asking, "When will I stop taking the injections?" At the same time, the child's father took time to accept the diagnosis. Similarly, the maternal parent of Pt. 2 shared, "It was like my whole world stopped when I heard the diagnosis." Such statements reflect the overwhelming shock felt by the family experiencing grief.

Despite these emotional challenges, many parents reported drawing their strength from religious beliefs. For example, Pt. 1's mother expressed, "Alhamdulillah, I accepted it and believed the treatment would help," and Pt. 2's mother thanked God upon learning of the diagnosis. Similarly, the parent of Pt. 8 said, "We just said this is Allah's will, and we need to be patient." These expressions of faith serve as vital emotional anchors amid the uncertainty.

Additionally, families described the emotional toll of the ongoing care. Weekly ERT, which is intrusive and painful, further exacerbated psychological exhaustion. The sibling of Pt. 9 reflected, "The needles make you feel psychologically tired, and the needle prick causes fatigue and tension for all of us." Parents often experience emotional distress in their children, including confusion and sadness. For example, the Pt. 8's father recalled, "He asked: 'Why me?'... I kept this matter to his mother," and Pt. 3's mother shared, "My son kept asking why he couldn't play like other kids."

These experiences highlight the ongoing emotional strain that parents experience as they manage their fears and try to keep their lives normal for their children. Although some received support from compassionate medical staff or schools with teaching assistants, "The school provided a worker... this is

a positive step,” others lacked enough outlets for emotional release, depending mainly on their own resilience and faith.

Subtheme 4.2: Absence of Integrated Psychological Support Services

Despite clear psychological stress, formal mental health support services were missing from the care process. Most parents expressed the need for emotional and mental health support for themselves and their children; however, they were uncertain about where or how to access these services. For instance, the Pt. 4’s mother openly said, “I don’t know who is responsible for providing psychological support, but honestly, sometimes I need [it] for myself and my son.”

Other families also expressed concerns regarding the impact of the disease on their social lives and the emotional development of their children. For example, the Pt. 8’s father mentioned that his wife “cried frequently and was deeply upset” after the diagnosis, and said, “We face emotional struggles as we are new to this rare disease; we don’t know anything about it.” These feelings of helplessness and isolation were common, emphasising the need for structured psychosocial support as part of managing RDs.

Furthermore, some families reported challenges related to bullying or social exclusion, which elevated their emotional stress. One family transferred their child to a private school because of concerns regarding bullying, reflecting not only emotional reasons but also financial strain. Moreover, the impact of the disease went beyond education; when asked about having more children, the family emphasised the combined cost of enrolling two children in private schools and hiring a domestic helper to assist with household and caregiving duties, which made it financially impossible. This highlights how the psychological and financial pressures of caring for a child with MPS-VI can affect family planning and household dynamics.

Collectively, these cases highlight the systemic oversight in addressing the mental health of both the patients and their parents. Although the physical aspects of treatment were well-managed, the lack of integrated mental health services significantly affects the families, to face substantial emotional challenges alone. In response, some parents developed creative, personal ways to support their child's emotional well-being. For example, the mother of Pt. 7 recalled using art to help her son cope with body image issues. “As one day he asked me about his hands, I told him you have ‘an art hand,’ and I brought him an art instructor,” she explained. Moreover, the parent stated that “He drew with calligraphy, with a napkin, and with a brush. I would keep telling him, ‘Look, your hands are an artist’s hands, your hands are the hands of an artist, so an artist’s hands are different.’” These efforts culminated in a personal art show where Pt. 7 proudly displayed the drawings, representing an empowering milestone that highlighted the importance of self-expression in emotional coping.

These accounts highlight the crucial role of non-medical interventions in promoting resilience and emotional well-being in patients with MPS-VI. Addressing these unmet needs through integrated

psychological counselling, peer support programs, and educational initiatives may significantly enhance families' overall care experiences for MPS-VI.

Discussion

To the best of our knowledge, this is the first study to comprehensively assess the clinical progression, treatment outcomes, and lived experiences of patients with MPS-VI treated at KFMC, a leading tertiary healthcare centre in SA. Notably, the demographic profile revealed a high rate of parental consanguinity, with all participating families having CMs primarily between first cousins. This genetic pattern significantly contributed to the increased prevalence and familial clustering of MPS-VI observed in the present cohort, with multiple affected siblings in some families.

Many studies have confirmed the high prevalence of consanguinity in SA (national rates: 56–58%), with first-cousin marriages being the most common. ^(36, 37) The findings of this study provide a basis for global research on the link between consanguinity and elevated rates of autosomal recessive disorders. ⁽³⁸⁾ Additionally, they provide a context for the early onset of symptoms and variability in diagnostic and treatment timelines. To address these issues, targeted genetic screening, premarital counselling programs, and community-level awareness campaigns are warranted, particularly in high-risk regions.

In the present study, quantitative analysis revealed substantial interpatient variability in ERT outcomes. Notably, all the children showed gains in height and weight, with an average increase of 17.2 cm in height. Moreover, these gains were more pronounced in patients who initiated therapy earlier and maintained it for a longer duration. However, despite these gains, most patients could not achieve the age-matched height norms, indicating MPS-V-associated irreversible skeletal changes. ⁽³⁹⁾ These findings support previous international evidence and highlight the importance of early and sustained ERT in optimising growth outcomes. ^(11, 24, 40)

Similarly, the 6MWT results showed improvements in functional endurance, indicating that most patients benefited from ERT, with an average distance gain of approximately 75 m. This change is consistent with findings from international multicentre studies reporting a similar increase. ^(6, 35) However, some children in the present study continue to experience exertional limitations such as fatigue and shortness of breath, indicating that although ERT improves function, it does not fully normalise the physical capacity. ⁽⁴⁾ Herein, no precise dose–response trend was observed in 6MWT performance across different treatment durations, suggesting the presence of a ceiling effect or individual variability.

Although these objective findings present clear therapeutic benefits of the interventions, they do not fully explain the variability in patient outcomes. Therefore, the challenges faced by families were incorporated into this study to better understand these discrepancies and gain insights through interviews. The qualitative findings enriched the quantitative data by uncovering the systemic, institutional, and emotional factors that shaped the diagnostic and treatment experiences, thereby generating four main themes that helped explain the delays, disruptions, and emotional burden highlighted in the quantitative

phase. These themes were as follows: (1) Diagnostic and Care Provision Inequities, (2) Treatment Pathways and Continuity of Therapy, (3) Logistical Burdens and Care Coordination Gaps, and (4) Psychosocial and Emotional Strain.

To visually integrate quantitative clinical outcomes with qualitative patient and family findings, Fig. 2 summarises how ERT-related benefits, diagnostic delay, treatment continuity, logistical barriers, and psychosocial strain intersect throughout the MPS VI care journey.

Figure 2: Patient and family perspectives on MPS VI in SA: integration of quantitative outcomes and qualitative insights. Illustrating how delays in diagnosis, ongoing treatment issues, logistical and financial obstacles, and psychosocial stress influence the MPS VI care pathway in Saudi Arabia.

Notably, the first theme, delayed diagnosis, was closely related to the timing of ERT initiation. Despite early symptom onset, families described journeys lasting many years, often exceeding 2 years, with some cases extending even longer. This is consistent with findings from regional studies of RD populations, including those on LSD, in the Middle East and North Africa, where diagnostic delays have been shown to range from 2 months to 14 years, with an average of approximately 25 months. ⁽⁴¹⁾ Additionally, a median diagnostic delay of 2.5 years has been reported among patients with MPS-VI. ⁽⁴²⁾ This delay emphasises global challenges, as it significantly impacts clinical outcomes, warranting early therapeutic intervention to prevent disease progression.

The experiences of parents revealed that misdiagnoses, inconclusive tests, limited knowledge among general practitioners (GPs), and fractured referral systems were the most common reasons for prolonged diagnostic journeys. Anderson et al. ⁽⁴³⁾ have reported similar findings in Australia regarding the diagnostic journey of families with RDs. They found that 38% of cases involved three to five physicians, 14% involved 6 to 10 physicians before receiving a diagnosis, and 43% noted perceived delays, highlighting the widespread nature of diagnostic odysseys in RDs. Furthermore, families emphasised the urgent need for better education of family medicine practitioners and more efficient specialist referral processes. ^(44, 45)

Regarding the second theme, representing treatment pathways and continuity, the findings highlighted that, despite a confirmed diagnosis and strong parental adherence to ERT, enrolled families consistently encountered systemic challenges that disrupted care continuity. These reported barriers include administrative bottlenecks, complex non-formulary procurement procedures, delays in drug preparation and pharmacy coordination, supply interruptions, and inconsistencies in dosing protocols. These operational inefficiencies could delay the treatment for several months, particularly between diagnosis and ERT initiation. This delay was attributed to a decrease in clinical gains, as reflected in quantitative indicators such as growth metrics and 6MWT performance.

Overall, these findings align with the existing literature, which reports similar access-related challenges in RD management. For instance, Wilcox et al. reported that Canadian families caring for patients with LSDs faced lengthy approval processes, delayed medication delivery, and fragmented communication

between institutions, which often led to substantial emotional distress and treatment disruption. ⁽⁴⁶⁾ Additionally, a multi-country study across Latin America identified similar structural barriers to the management of MPS-IVA and -VI, emphasising the need for efficient administrative systems, dependable drug supply chains, and decentralised care models to enhance treatment access and sustainability. ⁽¹⁵⁾

Altogether, these insights highlight the critical role of effective pharmacy management and coordinated procurement systems in ensuring uninterrupted access to ERT. Furthermore, these findings underscore the need to reform the targeted health system in SA. These reforms should focus on streamlining procurement procedures, enhancing coordination among hospital pharmacies, pharmaceutical manufacturers, and authorised drug distributors, and expanding regional infusion infrastructure. Such interventions are crucial to minimise treatment disruptions and optimise long-term clinical outcomes in patients with RDs. ⁽²⁰⁾

Accessibility and logistical challenges, including long travel distances, high accommodation costs, and disruptions in employment and education, comprised the third theme and pose significant hurdles for families living outside major urban areas. ^(15, 47) Moreover, due to inconsistency, home infusion therapy presented various disparities in healthcare access, despite being recommended internationally to address these issues. ^(6, 20, 48)

Geographic inequalities have emerged as critical determinants of the quality of care. In the present study, families residing outside Riyadh reported substantial logistical challenges and additional financial pressures that were not evident in the EMR data but were vividly described during interviews. These findings align with those of previous studies, emphasising the importance of decentralised infusion services in enhancing treatment adherence and alleviating family members' burden. ⁽¹⁾ Although some families supported the idea of home infusion, they experienced unequal treatment as this service was only offered to patients living outside the capital city, potentially affecting long-term adherence and outcomes.

Notably, international data have revealed similar disparities in access to ERT. For example, after the commercialisation of ERT in Mexico, patients with MPS-IVA faced an average delay of approximately 2 years before receiving their first infusion. In contrast, patients in Colombia were treated within 1 year of diagnosis. ⁽¹⁵⁾ Such differences highlight the regions' healthcare infrastructure and policy implementation, as well as the effects of timely access to treatment, further emphasising the need for equitable service provision.

Additionally, the psychosocial and emotional burden on parents further exacerbates the disease complexity, starting with the initial shock of diagnosis, followed by anxiety and stress regarding the uncertainty of disease progression, ongoing caregiving responsibilities, social stigma, and a lack of adequate psychological support. These burdens were especially evident among families living in regions with limited awareness of RDs and poor access to counselling services.

The experiences of the families included in the present study align with the global evidence showing high psychological stress among parents of children with chronic illnesses. This is consistent with the data of 89% of caregivers in the US and 88% in the UK reporting anxiety and stress, with > 70% feeling isolated or emotionally unsupported. In addition to managing the child's medical needs, parents frequently assumed quasi-clinical roles, such as serving as treatment coordinators, information seekers, educators, and advocates, due to significant gaps in the health system's infrastructure and providers' familiarity with rare conditions. ^(49, 50)

In addition to the disease complexity, many parents in SA viewed their roles through cultural and religious obligations. ⁽⁵¹⁾ Parental motivations were found to be deeply influenced by faith-based values, which shaped their perceptions of illness, caregiving responsibilities, and medical decision-making. Herein, many participants described their caregiving role as a religious duty and spiritual test that reinforced their resilience despite limited external support. These findings are consistent with the literature and highlight how, in Middle Eastern and Islamic contexts, religious beliefs substantially inform caregiving expectations, health behaviours, and interpretations of suffering. ⁽⁵²⁾

Altogether, these findings emphasise the need for a comprehensive system-level approach that addresses both the clinical and psychosocial needs of the patients and families affected by MPS-VI. Specifically, efforts need to focus on decentralising genetic and metabolic services, enhancing education for primary care providers, strengthening pharmacy logistics and drug procurement systems, and integrating structured psychosocial support services into standard care pathways. Implementing these steps may promote more equitable, timely, and patient-centred care, thereby aligning SA's RD care infrastructure with international best practices.

Strengths and Limitations of the Study

This study presented several strengths. Herein, a sequential explanatory mixed-methods design was employed, combining quantitative clinical data with qualitative accounts from family members to provide a detailed understanding of the MPS-VI patient experience at a major tertiary care centre. Additionally, this approach enabled a deeper exploration of treatment outcomes and the systemic, logistical, and emotional challenges faced by the families involved. The real-world clinical setting at KFMC enhances the practical relevance of these findings. Culturally specific factors, such as consanguinity and religious coping, were addressed in this study, and their contributions to the necessary contextual depth were highlighted. Furthermore, EMR timelines were associated with firsthand stakeholder experiences, providing insights into policy development that could improve care delivery for RDs across similar healthcare systems.

However, this study had some limitations; its single-centre setting and small sample size limited the generalizability of the findings to other settings or populations. Nonetheless, KFMC is a recognised national centre of excellence for managing MPS-VI in SA, and regarding RDs, single-centre studies are often necessary to gain insights into their functioning. Notably, the retrospective nature of the

quantitative data may have been affected by missing or incomplete records, particularly regarding ERT administration and anthropometric measures. In a qualitative study, family members' responses may have been influenced by recall bias or social desirability, potentially underestimating the specific challenges individuals face. Finally, the lack of interviews with healthcare providers and system-level stakeholders limited the study's ability to fully understand the administrative and institutional factors behind treatment delays and access barriers. Despite these limitations, this study provides valuable insights that can inform policy and practice and enhance care for patients with MPS-VI.

Conclusions

This study highlights the therapeutic benefits of ERT in patients with MPS-VI treated at KFMC and demonstrates measurable improvements in growth and functional capacity. However, it also highlights the significant gaps in diagnostic, treatment, and support systems that affect the lived experiences of both patients and their family members. Furthermore, these findings emphasise the urgent need for an early and accurate diagnosis, prompt initiation, and consistent delivery of ERT, equitable access to regional care, and culturally sensitive psychosocial services. It is crucial to address these issues through targeted policy reforms, decentralising RD services, adopting multidisciplinary care models to enhance the QoL and long-term outcomes of individuals with MPS-VI in SA, and aligning national care standards with best practices.

Abbreviations

AAV	
adeno-associated virus	
EMR	
electronic medical record	
ERT	
enzyme replacement therapy	
HSCT	
haematopoietic stem cell transplantation	
IRB	
Institutional Review Board	
KFMC	
King Fahad Medical City	
LSD	
lysosomal storage disorder	
MOH	
Ministry of Health	
MPS	
mucopolysaccharidosis	
MPS-VI	

mucopolysaccharidosis type VI
PNU
Princess Nourah bint Abdulrahman University
SD
standard deviation
SI
semi-structured interview
uGAG
urinary glycosaminoglycan
6MWT
six-minute walk test

Declarations

Ethics approval and consent to participate

Ethical approval for this study was obtained from the Institutional Review Board of Princess Nourah bint Abdulrahman University, Riyadh, Saudi Arabia (IRB Log Number: 23-0447; approval date: 18 May 2023) and from the Institutional Review Board of King Fahad Medical City, Riyadh, Saudi Arabia (IRB Number: 24-532; approval date: 25 September 2024). All participants provided written informed consent before participation in the study and interviews. All procedures involving human participants were conducted in accordance with the relevant ethical guidelines and regulations and with the principles of the Declaration of Helsinki.

Consent for publication

Not Applicable

Availability of data and materials

Due to patient confidentiality and ethical restrictions, the clinical records and semi-structured interview data from this study are not publicly accessible. De-identified data can be obtained from the corresponding author upon reasonable request and with ethics approval.

Competing interests

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Authors' contributions

HAA and AM provided supervision on this study. GMA, HAA, and AM assisted with the study conception and design and revised the manuscript. GMA, MA, MS, MJ, and EF contributed to the data collection. GMA and HAA interpreted the results. HAA and AM approved the final version of the manuscript for publication and agreed to be responsible for all aspects of this study.

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Figures

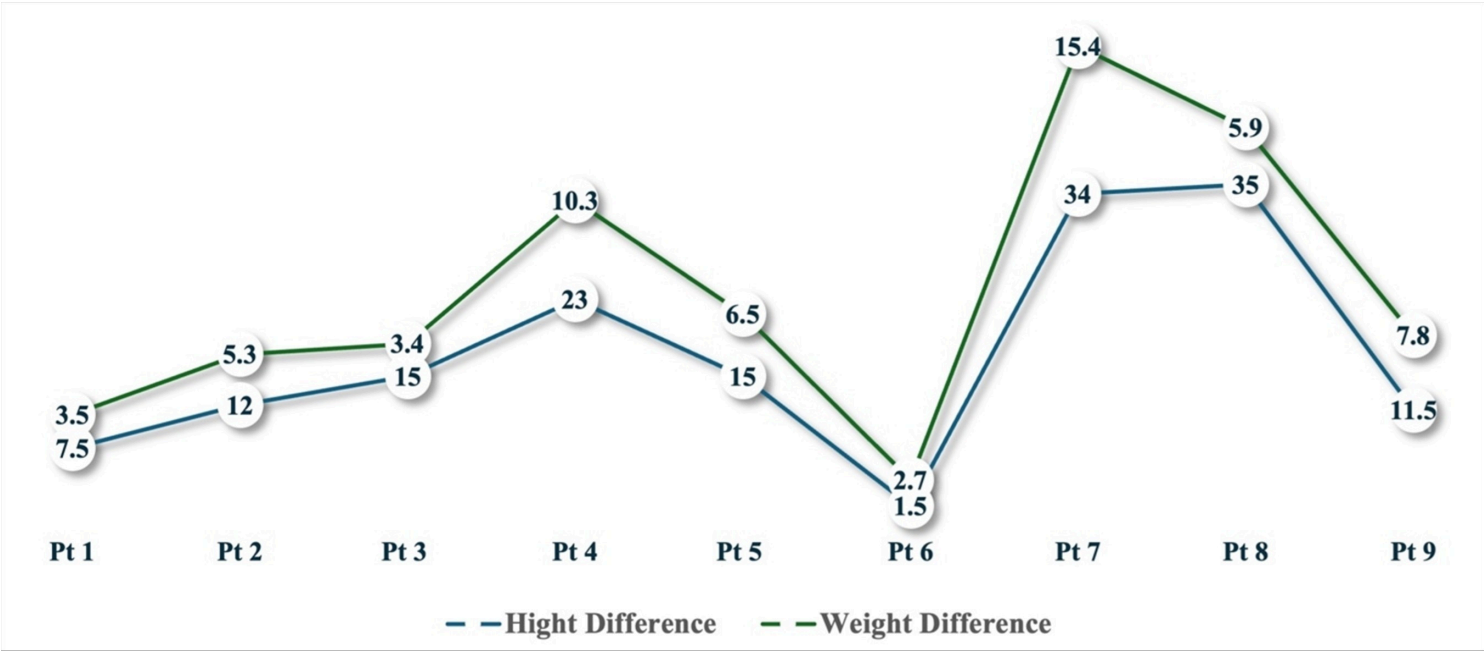


Figure 1

ERT duration versus height (ht.) and weight (Wt.) over 13 years. Descriptive trends showed that starting ERT earlier and maintaining it longer led to more significant anthropometric improvements.

Patient and Family Perspectives: MPS VI in Saudi Arabia

This case study explores the challenges faced by patients and families affected by mucopolysaccharidosis type VI (MPS VI), the most prevalent MPS subtype in Saudi Arabia.

Quantitative Findings

Delayed diagnosis
(avg. 2 years)



Mean diagnostic
avg. 2 years

+ 17,2 cm



+ 75 m
(6MWT)

Qualitative Themes



Diagnosis & Referral

Lengthy, uncertain
diagnostic processes



Treatment Continuity

Disruptions due to
supply & logistical issues



**Logistical/
Financial Burden**

Travel challenges,
additional expenses



Psychosocial Strain

High emotional load,
limited support



**Integration with
Systemic Gaps**

The findings connect with broader systemic issues such as diagnostic delays, fragmented care, and access barriers, highlighting the impact on treatment outcomes and family wellbeing.

Figure 2

Patient and family perspectives on MPS VI in SA: integration of quantitative outcomes and qualitative insights. Illustrating how delays in diagnosis, ongoing treatment issues, logistical and financial obstacles, and psychosocial stress influence the MPS VI care pathway in Saudi Arabia.

Supplementary Files

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