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Difficulties Associated with Enzyme Replacement Therapy for Mucopolysaccharidoses

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What is already known on this topic?

- *Mucopolysaccharidoses are severe multisystem disorders associated with high disease burden and caregiver burden.*
- *Enzyme replacement therapy (ERT), available for some types of mucopolysaccharidoses, requires weekly intravenous infusions and is difficult for patients and families.*

What this study adds on this topic?

- *Although most mucopolysaccharidosis patients miss 1 day of school or work every week, treatment compliance is high.*
- *Not receiving ERT is related to not being able to acquire it from abroad via the designated pharmacy.*
- *Unobtained ERT doses and ERT-related disruption to family life are associated with geographical factors.*

ABSTRACT

Background: Mucopolysaccharidoses are extremely rare, progressive, often severe multisystem disorders, some of which are managed by weekly intravenous enzyme replacement therapy. This study aimed to determine the difficulties faced by the patients with mucopolysaccharidosis and their families due to enzyme replacement therapy.

Methods: A questionnaire about demographics, enzyme replacement therapy-related characteristics, and specific enzyme replacement therapy-related difficulties was conducted over the telephone with mucopolysaccharidosis patients (or their parents) followed at a referral center in Turkey, who have been on enzyme replacement therapy for ≥12 months. The responses were analyzed with chi-square, Mann–Whitney *U*, Kruskal–Wallis tests, Spearman's rank correlation, and binary logistic regression.

Results: A total of 54 patients (median age: 13 years) participated, who had been receiving enzyme replacemnt therapy for a median of 5.02 years, 83.3% of whom had mucopolysaccharidosis-IVA or -VI. About 72.2% went to school or work, 64.1% of whom missed a full day every week due to enzyme replacement therapy. About 63% missed at least 1 dose in the past 6 months, mostly due to not being able to obtain doses or having intercurrent infections. Significantly more enzyme replacement therapy doses were missed or unobtained in Central (non-Ankara) and Eastern Anatolia, but enzyme replacement therapy-related disruption to family life was more severe in families living in Ankara.

Conclusions: We provide the first Turkish data about mucopolysaccharidosis patients' subjective enzyme replacement therapy experience, which is influenced by actionable inequalities and hurdles, partially related to geographical factors. Access to the drugs can be facilitated, and the clash of enzyme replacement therapy infusions with school and work should be avoided. Multi-center studies using more objective data sources are needed.

Keywords: Burden of disease, caregiver burden, enzyme replacement therapy, inborn errors of metabolism, lysosomal storage diseases, mucopolysaccharidosis, questionnaire, Turkey

INTRODUCTION

Glycosaminoglycans are important components of the extracellular matrix. They are degraded in lysosomes by specific enzymes, the inherited deficiencies of which give rise to a group of lysosomal storage diseases called mucopolysaccharidoses (MPSs), classified as MPS types I, II, III (subtypes IIIA-D), IV (subtypes IVA-B), VI, VII, and IX, based on the affected enzyme. Mucopolysaccharidoses are extremely rare with a total incidence of 1-5 in 100 000 live births.[1]

Mucopolysaccharidoses comprise a wide spectrum of severity and varying combinations of progressive multisystem involvement, with the severe forms associated with early mortality and low quality of life. Systemic manifestations include coarse facies, failure to thrive,

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developmental delay, intellectual disability, neurodegeneration, myelopathy, serous otitis media, hearing loss, corneal opacity, obstructive sleep apnea, restrictive airway disease, valvulopathy, cardiomyopathy, hepatosplenomegaly, joint stiffness and/or laxity, and skeletal dysplasia.[2] Symptomatic management by multidisciplinary experts is required for all types of MPS, but specific treatment targeting the underlying enzyme deficiency is only available as intravenous enzyme replacement therapy (ERT) in certain MPS types (weekly in MPS-I, II, IVA, and VI, biweekly in MPS-VII) and as hematopoietic stem cell transplantation (HSCT) in selected MPS-I patients.[2,3] While ERT improves or stabilizes cardiac dysfunction, obstructive sleep apnea, organomegaly, and endurance, it has little effect on growth, skeletal dysplasia, neurodegeneration, keratopathy, and pulmonary disease, which still account for significant morbidity and mortality.[3]

Enzyme replacement therapy is clearly a difficult treatment, but the personal difficulties of ERT is drastically understudied in comparison to the impact of the disease itself. In addition to the already high disease burden, patients and their families have to endure the difficulties brought on by ERT, including frequent travel to an infusion center, repeated intravenous cannula insertions (complicated by rough skin), absenteeism from school or work, and ERT-related adverse events. Furthermore, access to the ERT drug is not straightforward. At the time this study was performed, the only specific MPS treatment available in standard pharmacies and reimbursed by the Social Security Agency (SSA) in Turkey was indicated for MPS-I. Enzyme-related therapy for MPS-II, IVA, and VI were also reimbursed by the SSA, but the drugs were not available in pharmacies and had to be imported and dispensed for each patient via the Turkish Pharmacists' Association (TPA). Additionally, physicians had to apply to the Ministry of Health for permission to use the drug for each MPS-IVA patient and renew approval at intervals specified by the Ministry. The SSA began reimbursing ERT for MPS-VII (vestronidase) only recently in 2021.[4] Our study aimed to document the difficulties and associated factors related to ERT among MPS patients followed at a single center.

METHODS

Subjects

This was a cross-sectional questionnaire study conducted over the telephone in August-November 2018. It was approved by the Hacettepe University Ethics Board for Non-interventional Clinical Studies (GO 18/650-19). The participants consisted of MPS patients followed at our department who have been receiving ERT for at least 12 months at the time of the interview and provided informed consent as approved by the ethics board. Patients who received experimental treatments (e.g. gene therapy), were prescribed ERT with a non-standard regimen (e.g. tapering down after HSCT), or were obtaining the ERT drug via non-standard procedures (e.g. compassionate use program) were excluded.

The Questionnaire

Eligible patients were contacted over the phone, and the responding patient or parent was surveyed with a questionnaire including their demographic and medical characteristics, ERT history, missed or delayed doses of ERT in the past 6 months, and their problems about acquiring the drugs and accessing medical care to receive ERT. A "missed dose" was defined as not receiving the dose for that week, and a "delayed dose" was defined as receiving it within the week but later than the scheduled day. The level of disruption caused by ERT on the patient's and the family's daily life was assessed by a 5-point Likert scale (none, minor, neutral/unsure, moderate, or severe, corresponding to 1-5 points in order), reflecting the subjective view of the respondent.[5]

Statistical Analysis

Statistical analyses were performed with Statistical Package for the Social Sciences (SPSS) version 22.0 (IBM SPSS Corp.; Armonk, NY, USA). The qualitative data were expressed as numbers and percentages. Central tendencies were reported as mean ± SD or median as appropriate. Normality of the distributions was assessed with the Kolmogorov–Smirnov ($n \geq 50$) and Shapiro–Wilk ($n < 50$) tests (all non-normal). Numerical data from independent groups were compared by the Mann–Whitney *U* or the Kruskal–Wallis tests (for 2 or more groups, respectively). Post hoc pairwise comparisons after the Kruskal–Wallis tests used the Bonferroni correction for adjustment of the *P* value. Associations between 2 numerical variables were analyzed with Spearman's rank correlation and those between 2 categorical variables with chi-square test or Fisher's exact test, as dictated by the test conditions. $P < .05$ was accepted to be statistically significant. Variables independently associated with missed or delayed doses (0-1 dose vs. 2 or more doses) and with disruption to daily life (1-2 vs. 4-5 points on Likert scale) were analyzed with binary logistic regression using forward stepwise likelihood ratio, including variables found to be significantly associated in previous tests or variables of clinical interest (see "Results" section for details). Regression models were rejected if they failed to provide good fit for the actual data distribution (*P* value of the Hosmer–Lemeshow chi-square less than .05).[6]

RESULTS

Patient Characteristics

Fifty-four patients participated in the study, whose demographics are presented in Table 1. Mean age was 13.95 ± 7.35 years (median: 13.00, range: 1.40-33.87); 42 patients (77.8%) were younger than 18 years. The majority had MPS type IVA or VI (83.3%), did not have intellectual disability (88.9%), and regularly went to school or work (72.2%). They were mostly from Central Anatolia (40.8%, approximately two-thirds of whom came from Ankara, where our center is located), followed by Southeastern Anatolia (25.9%). They predominantly (94.4%) lived in cities, usually in provincial centers.

Enzyme replacement therapy-related characteristics are also summarized in Table 1. The mean age at initiation of ERT was 7.87 ± 6.50 years (median: 6.21, range: 0.40-26.41), and the mean ERT duration was 6.08 ± 3.10 years (median: 5.02, range: 1.00-12.40). All participants were prescribed weekly ERT. None had a central venous catheter, all requiring peripheral venous cannula placement for each infusion. In most patients (92.6%), the cannula could be placed in 1 or 2 attempts (mean: 1.46 ± 0.77 attempts, median: 1, range: 1-5). In total, 16 patients (29.6%) had a history of ERT-related adverse events, 12 of whom had non-life-threatening infusion reactions. Four

Table 1. Demographic and ERT-Related Characteristics of the Participants (N = 54)

Characteristics	n (%)
Demographics	
Female sex	24 (44.4%)
Questionnaire respondent	
Father	35 (64.8%)
Mother	17 (31.5%)
Self	2 (3.7%)
Diagnosis	
MPS-I	4 (7.4%)
MPS-II	5 (9.3%)
MPS-IVA	20 (37.0%)
MPS-VI	25 (46.3%)
Intellectual disability	6 (11.1%)
Attends school or has a steady job	39 (72.2%)
Current age (years)	
0-2	1 (1.9%)
2-5	3 (5.6%)
5-12	18 (33.3%)
12-18	19 (35.2%)
18-35	12 (22.2%)
Geographical region of residence	
Central Anatolia	22 (40.8%)
Ankara	15 (27.8%)
Other Central Anatolian province	7 (13.0%)
Southeastern Anatolia	14 (25.9%)
Black Sea Region	7 (13.0%)
Eastern Anatolia	6 (11.1%)
Aegean Region	5 (9.3%)
Administrative status of the place of residence	
Provincial center	40 (74.1%)
District center	11 (20.4%)
Smaller settlement (village, town)	3 (5.6%)
Household population	
2-3	9 (16.7%)
4-5	33 (61.1%)
6 or more	12 (22.2%)
ERT-related characteristics	
Age at initiation of ERT (years)	
0-2	7 (13.0%)
2-5	11 (20.4%)
5-12	25 (46.3%)
12-18	5 (9.3%)
18-35	6 (11.1%)
Duration of ERT (years)	
1-3	8 (14.8%)
3-6	26 (48.1%)
6-10	14 (25.9%)
> 10	6 (11.1%)
Peripheral IV access attempts per infusion*	
1	35 (64.8%)
2	15 (27.8%)
3-5	4 (7.4%)
ERT-related adverse events	
None	38 (70.4%)
Non-life-threatening infusion reactions	12 (22.2%)
Anaphylaxis	4 (7.4%)

*Approximate number as reported by the respondent. ERT, enzyme replacement therapy; IV, intravenous; MPS, mucopolysaccharidosis.

patients reported anaphylaxis to ERT, but they did not experience clinically relevant morbidity or mortality and were able to continue ERT after desensitization.

Enzyme Replacement Therapy Logistics and Access

Responses regarding the logistics of ERT and acquisition of the drugs are presented in Table 2. While 18.5% received their doses at our center, most of them received ERT in state hospitals (42.6%) or other university hospitals (27.8%) closer to their homes. They had to travel for a mean duration of 17.81 ± 13.34 minutes (median: 15, range: 0-60) to their infusion center. Out of 39 patients, 25 (64.1%) who went to school or work missed a full day every week due to ERT. The hospital companions of a minority of patients (27.8%) had a job, affected by half a day or a full day of absenteeism per week.

The difficulties related to acquisition of the drugs and disruptions to the weekly infusions were diverse (Table 2). A total of 63.0% reported missing at least 1 dose in the past 6 months, mostly due to not being able to obtain adequate doses (35.3%), followed by intercurrent acute infections (29.4%). Failure to obtain the drug was predominantly related to the TPA not acquiring and sending the drug in time (82.4%). A total of 35.2% reported delaying at least 1 dose in the past 6 months, mostly due to unavailability of hospital beds. Self-reported levels of disruption to daily living of the patient and of the family caused by ERT were found to be balanced across the 5-point Likert scale (mean: 3.02 ± 1.60, median: 3 points; and 3.11 ± 1.53, median: 3 points, respectively, Table 3).

Variables Associated With Dosing Alterations and Disruption to Daily Living

Correlations among the numerical and ordinal data revealed mostly statistically insignificant or significant but weak correlations ($P > .05$ or $P < .05$ but Spearman's $|\rho| < 0.40$, respectively). Statistically significant moderate or strong correlations ($|\rho|>0.60$ and $P < .05$) existed only between the levels of disruption to daily lives of the patients and that of the families ($\rho = +0.729$, $P < .001$) and between the numbers of missed and unobtained ERT doses ($\rho = +0.686$, $P < .001$). The number of missed doses in the past 6 months did not differ significantly by gender, the type of MPS, intellectual disability, the administrative status of the place of residence, the infusion center, going to school or work, disruption to the hospital companion's regular job, or a history of ERT-related adverse effects ($P > .05$) but differed significantly in relation to the geographical region of residence (Table 4). Similarly, the number of unobtained drug doses also differed significantly by the geographical region (Table 4) but not by gender, the type of MPS, intellectual disability, the infusion center, going to school or work, or a history of adverse effects ($P > .05$). The number of unobtained doses also differed significantly according to the administrative status of the place of residence ($P = .042$), which arose from the difference between provincial centers and small settlements (village, town) (0.48 ± 0.96 vs. 1.67 ± 0.58 doses in the past 6 months, respectively, adjusted $P = .044$).

Parameters associated with the levels of ERT-related disruption to the patient's life and to the family's life were investigated. While the reported disruption to the patient's life and the family life were strongly and positively correlated with

Table 2. ERT Logistics and Access (N = 54, Unless Indicated Otherwise)	
	n (%)
ERT infusion center	
State hospital	23 (42.6%)
University hospital other than ours	15 (27.8%)
Our university hospital	10 (18.5%)
Home	4 (7.4%)
Privately owned hospital	2 (3.7%)
Travel from home to infusion center (minutes)	
0 (Home treatment)	4 (7.4%)
2-10	16 (29.6%)
11-20	18 (33.3%)
21-30	11 (20.4%)
30-60	5 (9.3%)
Missed school or work days per week due to ERT (n = 39)	
Full day	25 (64.1%)
Half day	5 (12.8%)
None	9 (23.1%)
Hospital companion has a steady job	15 (27.8%)
Hospital companion's weekly missed work days due to ERT (n = 15)	
Full day	6 (40.0%)
Half day	9 (60.0%)
Number of missed ERT doses in the past 6 months	
None	20 (37.0%)
At least 1 dose	34 (63.0%)
1 dose	13 (24.1%)
2 doses	11 (20.4%)
3 doses	4 (7.4%)
4 doses	4 (7.4%)
5 doses	2 (3.7%)
Reasons for missing ERT doses (n = 34)	
Inadequate drug supply	12 (35.3%)
Infections	10 (29.4%)
Hospital bed unavailability	6 (17.6%)
Familial issues	3 (8.8%)
Non-infectious health issues	2 (5.9%)
Treatment non-compliance	1 (2.9%)
Reported difficulties with drug acquisition	
Delayed shipment of the drug from the TPA	18 (33.3%)
Obtaining a physicians' report for the drug	13 (24.1%)
Obtaining a drug prescription	6 (11.1%)
Approval from the Ministry of Health	5 (9.3%)
Submission of documents to the TPA	3 (5.6%)
Number of unobtained ERT doses in the past 6 months	
None	37 (68.5%)
At least 1 dose	17 (31.5%)
1 dose	6 (11.1%)
2 doses	6 (11.1%)
3 doses	4 (7.4%)
4 doses	1 (1.9%)
Reasons for inability of obtaining the drug (n = 17)	
Drug not being delivered from the TPA	14 (82.4%)
Not obtaining a physicians' report for the drug	1 (5.9%)
Delayed approval from the Ministry of Health	1 (5.9%)
Familial issues	1 (5.9%)

(*Continued*)

	n (%)
Number of delayed ERT doses in the past 6 months	
None	35 (64.8%)
At least 1 dose	19 (35.2%)
1-2 doses	13 (24.1%)
3-4 doses	3 (5.6%)
5 or more doses	3 (5.6%)
Reasons for dosing delays (n = 19)	
Hospital bed unavailability	9 (47.4%)
Familial issues	5 (26.3%)
Infections	4 (21.4%)
Non-infectious health issues	1 (5.3%)

ERT, enzyme replacement therapy; TPA, Turkish Pharmacists' Association.

Table 3. Self-Reported Disruption of Daily Life

	Level of Disruption to Daily Life Related to ERT (Points)					
	None (1)	Minor (2)	Neutral/Unsure (3)	Moderate (4)	Severe (5)	Total
Patient's life	15 (27.8%)	8 (14.8%)	6 (11.1%)	11 (20.4%)	14 (25.9%)	54 (100%)
Family's life	11 (20.4%)	12 (22.2%)	5 (9.3%)	12 (22.2%)	14 (25.9%)	54 (100%)

ERT, enzyme replacement therapy.

Table 4. Missed and Unobtained ERT Doses in the Past 6 Months and Disruption to Daily Living in Relation to Geographical Region (Mean ± SD)

	n	Missed Doses	Unobtained Doses	Level of Disruption to Patient's Life[a]	Level of Disruption to Family's Life[a]
All	54	1.35 ± 1.43	0.63 ± 1.07	3.02 ± 1.60	3.11 ± 1.53
Central Anatolia (not Ankara)	7	3.00 ± 1.29	1.71 ± 1.60	2.71 ± 1.80	2.71 ± 1.50
Eastern Anatolia	6	2.67 ± 1.03	1.67 ± 1.51	2.50 ± 1.64	2.17 ± 0.98
Ankara	15	1.13 ± 1.41	0.27 ± 0.46	3.60 ± 1.12	4.07 ± 1.34
Southeastern Anatolia	14	1.00 ± 1.18	0.36 ± 0.75	3.50 ± 1.70	3.43 ± 1.70
Aegean Region	5	0.60 ± 0.55	0.20 ± 0.45	2.00 ± 1.73	2.60 ± 0.89
Black Sea Region	7	0.29 ± 0.76	0.29 ± 0.76	2.29 ± 1.60	2.00 ± 1.56
P[b]		.001	.042	.166	.023

The number of missed doses is significantly higher in Central Anatolia (not Ankara) and Eastern Anatolia than the Black Sea Region ($P = .004$ and $P = .012$, respectively). Although the number of unobtained doses is higher in Central Anatolia (not Ankara) and Eastern Anatolia, pairwise comparisons do not show significant differences among regions after the Bonferroni correction. Similarly, while the level of disruption to family life related to ERT was higher in Ankara, the statistical significance of the differences did not persist after the adjustment of the *P* value by the Bonferroni correction. The other parameters depicted in the table were not significantly different. [a]On 5-point Likert scale (see "Methods" section). [b]Kruskal–Wallis test. ERT, enzyme replacement therapy.

each other (see above), they did not exhibit moderate or strong significant correlations with other numerical or ordinal variables. There were no significant differences in the levels of disruption to the patient's or the family's life in relation to MPS type, intellectual disability, gender, administrative status of the place of residence, patient's attendance to school or work, or the presence of adverse effects ($P > .05$). The level of disruption to family life differed significantly with regard to the geographical region (Table 4) and the infusion center ($P = .010$). The level of disruption to family life was significantly higher in those receiving ERT at our center (4.60 ± 0.52 points, n = 10) than those receiving ERT at state hospitals (2.96 ± 1.52 points, n = 23, adjusted $P = .049$) and at other university hospitals (2.40 ± 1.40 points, n = 15, adjusted $P = .005$). The level of disruption to the patient's own life did not differ significantly with regard to the geographical region ($P = .166$) or the infusion center ($P = .231$).

In binary logistic regression analysis, a model satisfying the predetermined requirements could not be constructed using the level of disruption to family life as the dependent variable. The models constructed for the level of disruption to the patient's life and for the numbers of missed and unobtained doses in the past 6 months are summarized in Table 5. The only statistically significant model with acceptable sensitivity, specificity, and accuracy was the one revealing the number of unobtained doses as the most important variable independently associated with the number of missed doses, but it could explain only 39.9% of the variance in the number of missed doses (Table 5).

DISCUSSION

The efficacy of ERT in MPS has been widely studied, including recent reports from Turkey.[7-10] Local information on demographic and clinical characteristics is also available.[11,12] However,

Table 5. The Most Important Variables Independently Associated With the Numbers of Missed and Unobtained Doses in the Past 6 Months and the Level of ERT-Related Disruption on the Patient's Life

Dependent Variable	Independent Variables	β Coefficient	Standard Error	P	Odds Ratio	95% CI
Level of disruption on patient's life*	Type of MPS (I-II with reference to IVA-VI)	−2.528	1.197	.035	0.080	0.008-0.834
	Geographical region (Ankara with reference to non-Ankara	2.592	1.155	.025	13.360	1.389-128.545
	Constant	0.007	0.355	.984	1.007	
Number of unobtained doses**	Geographical region (Central (non-Ankara) or Eastern Anatolia with reference to other regions)	3.009	0.827	<.001	20.267	4.004-102.588
	Constant	−2.539	0.600	<.001	0.079	
Number of missed doses***	Number of unobtained doses	2.185	0.845	.010	8.893	1.696-46.629
	Constant	−1.522	0.493	.002	0.218	

The models were constructed using binary logistic regression with forward selection likelihood ratio. Properties of the models were as follows: *Variables added to the model: age, gender, type of MPS, intellectual disability, geographical region, administrative status of place of residence, household population, infusion center, distance to infusion center, missed school or work days, number of venous access attempts, adverse events, numbers of missed, delayed, and unobtained doses. Overall accuracy: 64.6%, sensitivity: 100.0%, specificity: 26.1%, Nagelkerke $R^2 = .298$, $P = .002$. **Variables added to the model: Age, gender, geographical region, household population, type of MPS, administrative status of place of residence. Overall accuracy: 85.2%, sensitivity: 36.4%, specificity: 97.7%, Nagelkerke $R^2 = 0.377$, $P = .001$. ***Variables added to the model: age, gender, number of unobtained doses, type of MPS, geographical region, household population, administrative status of place of residence, distance to infusion center, missed school or work days, adverse events. Overall accuracy: 85.2%, sensitivity: 72.7%, specificity: 88.4%, Nagelkerke $R^2 = 0.399$, $P < .001$. ERT, enzyme replacement therapy; MPS, mucopolysaccharidosis.

only a single study by Zengin et al.[13] has addressed the difficulties of living with MPS in Turkey, based on interviews with parents of 10 children with MPS. Although their study was mainly concerned with the burden of the disease, themes coinciding with our study also emerged, including school attendance and difficulties in social life.[13] A German study on 10 MPS-VI patients with a Turkish background also addressed the difficulties and coping strategies but mainly in relation to the disease rather than the treatment.[14] To the best of our knowledge, ours is the first study from Turkey to investigate the difficulties related specifically to ERT in MPS. In a patient population mostly participating in social life (school or work), dominated by intellectually normal MPS-IVA and MPS-VI patients who had been on ERT for 1-12 years, we have demonstrated that compliance to ERT is fairly good (a mean of 1.35 ± 1.43 missed weekly doses in the past 6 months), but ERT experience is influenced by actionable inequalities and hurdles, which are partially related to sociodemographic factors.

A total of 64.1% of MPS patients who go to school or work miss an entire day every week due to ERT. High absenteeism from school or work has also been reported by Solano et al.[15] in MPS-IVA and VI patients from Latin America, but mostly due to disease burden and progression, and its relation to ERT was largely unexplored. In already disadvantaged patients with sensory, motor, and/or learning disabilities, 20% absence from school or work solely due to ERT should be avoided. A potential solution could be scheduling ERT after-hours or on weekends, which would require allocation of health care workforce. Since most patients do not have problems with intravenous access and adverse events are rare and manageable, home treatment is a viable option and can increase compliance.[16-18] Our data suggest that this might not be a priority because all patients receive ERT close to their home, and compliance is already high. However, it should be noted that this study was performed before the coronavirus disease 2019 pandemic, which has caused treatment interruptions and increased disease burden in our patients due to limited access to infusion centers.[19] In fact, the need to transfer ERT services to home has emerged in different parts of the world,[20,21] and could be considered in Turkey, as well.

Multiple statistical tools point to unobtained doses as the most significant cause of missing ERT, and this is largely related to delayed delivery from the TPA. As outlined above, access to the ERT drug is a multi-step process which might be hard for families to navigate. Licensing the drugs and making them available in local pharmacies could greatly ease and hasten the process of obtaining the ERT drugs. Patients living in Central Anatolia (in provinces other than Ankara) and Eastern Anatolia, especially in small settlements, have a disadvantage in obtaining drug doses and continuing ERT without interruption. The study by Solano et al.[15] has shown that ERT interruption due to temporary unavailability of the drug is similarly common in Latin America, but this did not differ significantly among urban and rural areas. It is possible that the apparent influence of geographical factors is confounded by economic, social, and cultural factors not addressed in our study and is probably only a part of well-known regional health disparities,[22] requiring broader socioeconomic and public health interventions for improvement.

It is interesting that in the questionnaire respondents reported a bidirectionally skewed subjective disruption to daily life of the patient and the family, with similar numbers of respondents stating that there is little to no disruption versus moderate to severe disruption (Table 3), again associated with the geographical region. It has been reported that cultural factors, including religious background, which were not explored in our questionnaire, can influence how Turkish families deal with MPS.[13,14] In fact, faith is a common coping mechanism for caregivers of chronic patients,[23] and its influence may apply to the burden of the treatment as well as that of the disease. This study suggests that in contrast to missing ERT doses, more disruption to family life is associated with receiving ERT infusions at our center. However, since most patients

from Ankara receive infusions at our center, it is difficult to differentiate whether receiving ERT at our center or living in Ankara is actually causative of the disruption to family life. Although the reasons for missing or delaying a dose are not significantly different between patients going to different infusion centers, a post hoc look at the data shows that 4 out of 6 patients who missed a dose and 4 out of 9 patients who postponed a dose in the past 6 months due to unavailability of hospital beds were those coming to our hospital for their weekly ERT, which necessitates a self-criticism and reevaluation of the capacity and functioning of our infusion unit. Even though missed or delayed doses were not significantly associated with disruption to family life, it can be argued that problems with scheduling a sick child's regular weekly treatment in a metropolis like Ankara can easily cause strain on family life. In fact, although caregivers in rural areas may have worse socioeconomic indices, they report similar emotional stress and better health than their urban counterparts,[24] which may be related to the numerous difficulties of living in a large city. Dedicated, flexible, patient- and family-friendly infusion centers in larger cities may alleviate the families' burden related to ERT.

Study Limitations

Our study has several limitations. Perhaps most importantly, since the data were gathered not from objective health records, but from questionnaire answers provided by the patients or their parents, the study is prone to recall bias and social desirability bias. The questionnaire was designed by the researchers and was not a validated tool. Although 54 is a substantial number of participants for such a rare disease group and reflects valuable experience from a single center, it is still too small a number to empower advanced statistical methods. We did not gather information on literacy, economic status, or quality of life, which could have contributed to more comprehensive data interpretation. On the other hand, quality of life is influenced greatly by the disease itself and could have steered away from the burden related to ERT, the actual focus of the study.

CONCLUSIONS

Despite its limitations, this study provides the first data about the ERT experience of Turkish MPS patients. While the geographic health disparities are concerning, there is also room for improvement in facilitating access to the drugs and circumventing the clash of ERT infusions with school and work. Multi-center studies using more objective sources and taking into account more data may overcome some of the limitations of this study.

Ethical Committee Approval: Ethics committee approval was received from the Hacettepe University Ethics Board for Non-interventional Clinical Studies (approval number: GO 18/650-19).

Informed Consent: Informed consent was obtained from all participants who participated in this study.

Peer Review: Externally peer-reviewed.

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REFERENCES

1. Puckett Y, Mallorga-Hernández A, Montaño AM. Epidemiology of mucopolysaccharidoses (MPS) in United States: challenges and opportunities. *Orphanet J Rare Dis.* 2021;16(1):241. [CrossRef]
2. McBride KL, Flanigan KM. Update in the mucopolysaccharidoses. *Semin Pediatr Neurol.* 2021;37:100874. [CrossRef]
3. Parini R, Deodato F. Intravenous enzyme replacement therapy in mucopolysaccharidoses: clinical effectiveness and limitations. *Int J Mol Sci.* 2020;21(8):2975. [CrossRef]
4. Sosyal Güvenlik Kurumu. Sağlık uygulama tebliği. *Resmi Gazete.* 2013;28579:9-378.
5. Likert R. A technique for the measurement of attitudes. *Arch Psych.* 1932;22:5-55.
6. Hosmer DW, Lemeshow S, Sturdivant RX. *Applied Logistic Regression.* 3rd ed. New Jersey: Wiley; 2013.
7. Bilginer Gurbuz B, Aypar E, Coskun T, et al. The effectiveness of enzyme replacement therapy on cardiac findings in patients with mucopolysaccharidosis. *J Pediatr Endocrinol Metab.* 2019;32(10):1049-1053. [CrossRef]
8. Kılavuz S, Basaran S, Kor D, et al. Morquio A syndrome and effect of enzyme replacement therapy in different age groups of Turkish patients: a case series. *Orphanet J Rare Dis.* 2021;16(1):144. [CrossRef]
9. Kılıç M, Dursun A, Coşkun T, et al. Genotypic-phenotypic features and enzyme replacement therapy outcome in patients with mucopolysaccharidosis VI from Turkey. *Am J Med Genet A.* 2017;173(11):2954-2967. [CrossRef]
10. Azak E, Gündüz M. Mukopolisakkaridoz tip VI'lı çocuklarda kardiyovasküler bulgular ve enzim replasman tedavisinin etkisi. *Trk Kardiyol Dern Ars.* 2019;47:587-593. [CrossRef]
11. Er E, Canda E, Kalkan Uçar S, Sözmen E, Çoker M. (Maroteaux-Lamy Sendromu) Tanılı Hastalarda Klinik deneyim. *J Pediatr Res.* 2016;3:82-85. [CrossRef]
12. Teke Kısa P, Köse E, Ateşoğlu M, Arslan N. Evaluation of demographic and clinical characteristics of patients with mucopolysaccharidosis. *J Pediatr Res.* 2017;4(2):59-62. [CrossRef]
13. Zengin M, Yayan EH, Akıncı A. Difficulties experienced by Turkish parents and their coping strategies: children with mucopolysaccharidosis. *J Pediatr Nurs.* 2020;53:e142-e148. [CrossRef]
14. Dilger H, Leissner L, Bosanska L, Lampe C, Plöckinger U. Illness perception and clinical treatment experiences in patients with M. Maroteaux-Lamy (mucopolysaccharidosis type VI) and a Turkish migration background in Germany. *PLoS One.* 2013;8(6):e66804. [CrossRef]
15. Solano VM, Mandujano CYC, Avila-Rejon CA, Espin VH, Montaño HPQ. Disease burden, management patterns and multidisciplinary clinical approaches for patients with MPS IVA and VI in selected Latin American countries. *Mol Genet Metab Rep.* 2021;28:100769. [CrossRef]
16. Bagewadi S, Roberts J, Mercer J, et al. Home treatment with Elaprase and Naglazyme is safe in patients with mucopolysaccharidoses types II and VI, respectively. *J Inherit Metab Dis.* 2008;31(6):733-737. [CrossRef]

17. Burton BK, Wiesman C, Paras A, Kim K, Katz R. Home infusion therapy is safe and enhances compliance in patients with mucopolysaccharidoses. *Mol Genet Metab*. 2009;97(3):234-236. [CrossRef]
18. Finnigan N, Roberts J, Mercer J, Jones SA. Home infusion with Elosulfase alpha (Vimizim®) in a UK Paediatric setting. *Mol Genet Metab Rep*. 2018;14:15-18. [CrossRef]
19. Kahraman AB, Yıldız Y, Çıkı K, et al. Invisible burden of COVID-19: enzyme replacement therapy disruptions. *J Pediatr Endocrinol Metab*. 2021;34(5):539-545. [CrossRef]
20. Pal S, Bhatia S, Bijarnia-Mahay S, Verma IC, Puri RD. Challenges in chronic genetic disorders: lessons from the COVID-19 pandemic. *Indian Pediatr*. 2021;58(4):391-392. [CrossRef]
21. Sechi A, Macor D, Valent S, et al. Impact of COVID-19 related healthcare crisis on treatments for patients with lysosomal storage disorders, the first Italian experience. *Mol Genet Metab*. 2020;130(3):170-171. [CrossRef]
22. Hacettepe Nüfus Etütleri Enstitüsü. *2018 Türkiye Nüfus ve Sağlık Araştırması*. Ankara: Hacettepe Üniversitesi Nüfus Etütleri Enstitüsü, T.C. Cumhurbaşkanlığı Strateji ve Bütçe Başkanlığı, TÜBITAK; 2019.
23. Bialon LN, Coke S. A study on caregiver burden: stressors, challenges, and possible solutions. *Am J Hosp Palliat Care*. 2012;29(3):210-218. [CrossRef]
24. Crouch E, Probst J, Bennett K. Rural-urban differences in unpaid caregivers of adults. *Rural Remote Health*. 2017;17(4):4351. [CrossRef]