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EFFECTS OF ENZYME REPLACEMENT THERAPY ON QUALITY OF LIFE, FUNCTIONAL INDEPENDENCE AND AEROBIC CAPACITY IN CHILDREN WITH MUCOPOLYSACCHARIDOSIS

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Abstract: The mucopolysaccharidosis (MPS) can lead to poor endurance and mobility, often associated with pain, restricted range of motion (ROM), low energy levels and fatigue, negatively affecting quality of life and activities of daily living. This study aimed to examine the impact of enzyme replacement therapy (ERT) on aerobic capacity, functional independence and quality of life in children with MPS and to determine the anxiety and depression levels of their caregivers. Study Design established in Cross sectional study. Twelve children aged 3 to 11 years were included in the study. The subjects were divided into two groups according to the use of ERT. Quality of life and functional independence were assessed using the Pediatric Quality of Life Inventory (PedsQL) and Functional Independence Measure for Children (WeeFIM). The 6-minute walk test (6MWT) and timed up and go test (TUG) were used to evaluate aerobic capacity. Anxiety and depression levels of parents were assessed using the Beck Anxiety Inventory (BAI) and Beck Depression Inventory (BDI), respectively. A total of 12 MPS patients 7 boys (58.3%) and 5 girls (41.7%) with a mean age of 5.58±2.67 years were included in the study.1 patient had MPS type I, 2 patients had MPS type III, 5 patients had MPS type IV, and 4 patients had MPS type VI. Six patients were receiving ERT. The children had a mean 6MWT score of 330.83±114.29, a mean TUG score of 14.24±5.71 sec, a mean PedsQL score of 46.83±14.03 and a mean WeeFIM score of 70.83±26.85. Their caregivers had a mean BAI score of 19.25±10.95 and a mean BDI score of 19.41±6.81. A significant difference was found between the children receiving ERT and those not receiving in the WeeFIM scores ($P<0.05$); other parameters were comparable between the groups ($P>0.05$). ERT did not change aerobic capacity and quality of children with MPS but increased their level of functional independence. Multisystem involvement in MPS children may affect anxiety and depression levels of their caregivers but ERT does not seem to have any effect on this psychosocial aspect.

Keywords: Mucopolysaccharidosis, Aerobic capacity, Quality of life, Functional independence

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1. Introduction

Mucopolysaccharidosis (MPS) is a rare, inherited lysosomal storage disease characterized by accumulation of glycosaminoglycan (GAG) in tissues as a result of deficiency of lysosomal enzymes. It occurs in approximately 1 in 25,000 live births and 7 distinct forms of MPS have been identified (Zhou et al., 2020).

MPS causes chronic, progressive systemic disorders due to enzyme deficiency. Musculoskeletal manifestations of MPS include bone and vertebral deformities, restricted joint function and ROM (range of motion), rib cage abnormalities, short stature and hip dysplasia as well as flexion contracture in the knee and interphalangeal joints and joint laxity (Yıldız et al., 2016). Individuals with MPS may develop obstructive respiratory disorders such as obstructive sleep apnea due to narrowing of the airways, especially in the upper respiratory tract, as a result of GAG accumulation. Vision (corneal clouding, glaucoma, retinal degeneration) and hearing problems can also occur. Cardiovascular disorders may be seen and as with other systemic conditions, cardiovascular symptoms are progressive and have a significant impact on the aerobic capacity of the patients (Mohan et al., 2002). The accumulation of glycosaminoglycans in the central nervous system may cause mental and neurocognitive effects and neuropathy may develop due to spinal cord compression arising from spinal canal stenosis due to

GAG deposition. The nervous system is commonly affected in some types of MPS, directly caused by nerve root and/or spinal nerve compression and can lead to cognitive impairment (Zhou et al., 2020).

Clinical manifestations of MPS can lead to poor endurance and mobility, often associated with pain, restricted range of motion (ROM), low energy levels and fatigue, negatively affecting quality of life and activities of daily living. MPS patients may experience reduced participation in school, work and social life, increased physical and emotional dependence on family and friends, low self-esteem, and psychological, behavioral and mental health conditions such as depression and anxiety (Hendriksz et al., 2016). In addition, chronic illnesses are an important source of stress for both the child and their family. It is known that in any chronic illness not only on the child but also on all members of the family can be negatively affected emotionally and economically.

Currently, there is no treatment that cures the symptoms of MPS. However, there are some forms of treatment that can delay the progression of the disease (Heese, 2008). Enzyme replacement therapy (ERT) is one such treatment and used for the management of some subtypes of MPS disease. ERT is based on the concept of replacing the missing enzyme in the circulation to prevent the build-up of glycosaminoglycan (GAG) in the tissues (Wraith, 2006). ERT directly supplements the body with a functional enzyme to lower or normalize GAG levels (Zhou et al., 2020). ERT is known to have limited effects on the brain and avascular cartilage (Valayannopoulos et al., 2011).

Very few studies in the literature have examined the impact of MPS in the lives of children affected by this disease. Studies investigating functional capacity, independence and quality of life in children receiving or not receiving ERT have not provided a clear picture of the problems faced by these children. Secondly, psychological problems experienced by caregivers of children with MPS have not been studied specifically in former studies. Therefore, the aim of this study was to examine the impact of ERT on aerobic capacity, functional independence and quality of life in children with MPS and to determine the anxiety and depression levels of their caregivers.

2. Material and Methods

2.1. Subjects

Twelve children with MPS who were followed at the pediatric metabolism disorders outpatient clinic from April to December 2020 were included in the study. The study inclusion criteria were age between 3 and 11 years and having a diagnosis of MPS. Patients refusing to participate in the study, patients without a definite diagnosis and patients, parents who did not cooperate with the study tests, patients who have had surgical operations on upper and lower extremities and who have already had physical therapy were excluded from the study.

Physical and demographic characteristics of the subjects were recorded at the beginning of the study. The subjects were divided into two groups according to ERT use. Quality of life and functional independence scales were completed individually for cooperative children and with parents for non-cooperative children. The Beck Anxiety Inventory and Beck Depression Inventory were completed by caregivers themselves and they do not have any treatments and chronic diseases.

2.2. Study Assessments

2.2.1. Pediatric quality of life inventory

The Pediatric Quality of Life Inventory (PedsQL) is a health status instrument developed by Varni et al. for the assessment of health-related quality of life in children and adolescents from 2 to 18 years of age (Varni et al., 2001). The PedsQL can be completed by children themselves or with their parents. The tool consists of a total of 23 questions that assess physical functioning (8 questions), emotional functioning (5 questions), social functioning (5 questions), and school functioning (5 questions). Possible maximum scores range between 0 and 100 and higher scores indicate better quality of life.

2.2.2. Functional independence

Functional independence of the subjects was assessed using the Functional Independence Measure for Children (WeeFIM). It is a short and validated tool to determine impairment of developmental, educational and social functioning in children with cerebral palsy and other developmental disorders (Erkin et al., 2001). The WeeFIM is an 18-item scale that measures the performance of the child in activities of daily living including bowel and bladder control, transfers, mobility, communication, eating, grooming, bathing, upper body dressing, lower body dressing, toileting and social cognition. Each item is assigned a score between 1 and 7 points. Higher total scores indicate greater level of independence.

2.2.3. Aerobic capacity

Aerobic capacity was assessed using the 6-minute walk test (6MWT) and timed up and go (TUG) test. For the 6MWT test, the subjects were asked to walk but not run for 6 minutes on a 30-meter corridor as fast as possible. Care was taken not to change the pace. At the end of the test, total distance covered was measured (Özalevli et al., 2011).

The TUG test is a practical test that allows quick assessment of dynamic balance, gait speed and mobility. During the test, the subjects were asked to stand up from a chair without holding on to the arms of the chair, walk 3 meters, turn, return to the chair without touching anything and sit down again. Total time was recorded in seconds (Williams et al., 2005).

2.2.4. Functional reach test

The modified functional reach test was developed by Lynch et al. to evaluate dynamic balance of the trunk. It is a reliable and validated test to measure the distance an individual can reach forward without losing balance

while sitting in a fixed position (Lynch et al., 1998). For the test, the subjects were instructed to sit with the arm kept parallel to the wall and shoulder flexed to 90 degrees and measurement was taken from the distal end the third metacarpal. Then, they were asked to reach forward as far as possible without changing their position and the end position that they could reach was marked. The difference between the start and end positions was measured by a measuring tape and recorded in centimeters.

2.2.5. Beck depression inventory

The Beck Depression Inventory (BDI) was used to determine the depression level of caregivers. The BDI was developed for measure the risk of depression, the level of depressive symptoms and changes in the severity of depression in adults. Reliability and validity of a Turkish version of the BDI were demonstrated by Hisli (1989). The BDI is a 21-item, self-rated scale and each item is scored between 0 and 3 points. Higher total scores indicate greater depression severity.

2.2.6. Beck anxiety inventory

The Beck Anxiety Inventory (BAI) was used to evaluate the anxiety level of caregivers. The BAI was developed for determine the frequency of anxiety symptoms experienced by individuals. It is a 21-item, Likert scale with scores ranging from 0 and 3 points. Higher overall scores denote greater level of anxiety. Reliability and validity of a Turkish version of the BAI were demonstrated by Ulusoy et al. (1998).

2.3. Statistical Analysis

The data were analyzed using the SPSS software, version 23.0 (SPSS Statistics for Windows, IBM Corp. Armonk, NY). Descriptive statistics were presented as mean ± standard deviation (SD) for continuous variables and as number (n) and percentage (%) for numerical data. The Kolmogorov-Smirnov test was used to check whether the data followed a homogeneous distribution. The non-parametric Mann-Whitney U test was used to compare outcomes between the study groups. The statistical significance level was set at $P<0.05$.

3. Results

The mean age of 12 children (5 girls, 7 boys) included in the study was 5.58±2.67 years. Four children who did not meet age criteria were excluded from the study. There were 1 patient diagnosed with MPS type I, 2 patients with MPS type III, 5 patients with MPS type IV, and 4 patients with MPS type VI. Demographic and physical characteristics of the patients are summarized in Table 1.

Six patients were receiving ERT once a week and 6 patients were not. Similar physical characteristics were observed when the two groups were compared according to the ERT use ($P>0.05$) (Table 2).

Statistically, only WeeFIM scores were significantly different between children receiving or not receiving ERT ($P<0.05$). The two groups were comparable in all other parameters ($P>0.05$) (Table 3).

All caregivers were mothers. The mean ages were 34.64 years for the caregivers, 33.00 years for mothers of children receiving ERT and 35.33 years for mothers of children not receiving ERT. No significant difference was found between the mothers of children receiving or not receiving ERT in terms of depression and anxiety levels ($P>0.05$).

4. Discussion

In this study aiming to determine the aerobic capacity, functional independence and quality of life in children with MPS and anxiety and depression levels in their caregivers, greater functional independence was found in children receiving ERT than in children not receiving ERT.

Table 1. General characteristics of the patients

	D	Age (mth)	ERT reception	Age (y)	ERTSA (mth)	H/W (cm/kg)	S	PedsQL	WeeFIM	FR (cm)	6MW (m)	TUG (sec)
1	Type IV	32	No	3	-	80/10.5	M	52	44	8	310	11.50
2	Type III	30	No	5	-	111/27	M	49	46	10	340	16.44
3	Type I	88	Yes	8	88	114/23	F	21	118	16	540	12.34
4	Type IV	21	Yes	3	21	82/11	M	31	69	7.5	300	15
5	Type IV	24	Yes	5	24	100/13	F	34	110	12	360	9
6	Type VI	11	Yes	7	11	93/13	M	51	93	13	430	10.77
7	Type IV	30	Yes	3	30	85/11.5	M	51	55	7	70	31
8	Type IV	32	No	3	-	87/10.7	F	36	85	17	360	11
9	Type VI	30	Yes	9	30	93/16	F	70	77	8	320	11.66
10	Type VI	20	No	3	-	85/11	M	47	55	7	240	15.75
11	Type VI	37	No	6	-	93/12	F	57	67	15	280	12.5
12	Type III	114	No	11	-	136/32.8	M	63	31	15	420	14

D= diagnosis, mth= month, y= year, ERTSA= enzyme replacement therapy, ERTSA= enzyme replacement therapy starting age, H/W= height /weight, S=sex, M= male, F= female, PedsQL= pediatric quality of life inventory, WeeFIM= functional independence measure for children, FR= functional reach, 6MW= 6 minute walk, TUG= time up go.

Table 2. Physical characteristics of the groups by ERT use

	Total (n=12)	ERT users (n=6)	Non-ERT users (n=6)		
	X± SD	X± SD	X±SD	z	P
Age (y)	5.58±2.67	6.00±2.37	5.17±3.13	-0.816	0.414
Height (cm)	96.58±16.48	94.50±11.50	98.67±21.21	-0.081	0.936
Body weight (kg)	15.93±7.41	14.58±4.48	17.28±9.83	-0.562	0.574
Age at diagnosis (mth)	39.08±30.24	34.00± 27.37	44.17±34.67	-1.292	0.196

mth= month, y= year

Table 3. Comparison of functional independence, quality of life and aerobic capacity between the groups

	Total (n=12)	ERT users (n=6)	Non-ERT users (n=6)		
	X± SD	X± SD	X±SD	z	P
PedsQoL (score)	46.83±14.03	43.00±17.70	50.67±9.22	-0.962	0.336
WeeFIM (score)	70.83±26.85	87.00±24.39	54.67±19.09	-2.166	0.030
6MWT (sec)	330.83±114.29	336.67±157.06	325.29±63.17	-0.561	0.575
TUG (sec)	14.24±5.71	14.96±8.10	13.53±2.25	-0.641	0.522
Functional Reach (cm)	11.33±3.62	10.75±3.84	11.92±3.64	-0.723	0.470
Caregiver					
BDI (score)	19.41±6.81	17.33±4.59	21.50±8.41	-0.647	0.517
BAI (score)	19.25±10.95	19.33±12.21	19.17±10.72	-0.321	0.748

6MWT= 6 minute walk test, TUG= timed up and go, BDI= beck depression inventory, BAI= beck anxiety inventory.

Early initiation of ERT has been associated with increased survival as well as positive effects on respiratory function (Broomfield et al., 2020). Functional independence is reduced in children with MPS due to joint deformities, mental-cognitive impairment, neuropathy, and sleep disorders including obstructive apnea and continuous hypoventilation (Lopes et al., 2019). Earlier introduction of ERT in MPS patients may improve disease course in the long-term or prevent permanent damage (Muenzer, 2011). Although early diagnosis and initiation of ERT do not reverse orthopedic and musculoskeletal problems and developmental retardation, it can slow the rate of disease progression (Barak et al., 2020). In our study, ERT did not result in a difference in motor functions of the patients as assessed by 6MWT, TUG and functional reach tests and only functional independence level was higher in children receiving ERT. It is not understandable why increased independence level was not reflected in the objective measures of functional capacity and quality of life. This may be due to the differences in the number of items and scoring of the WeeFIM tool, which is commonly used in pediatrics and was deemed suitable for the age group examined in the present study as compared with the PedsQL. Therefore, it may be important to use scales with a wider range of questions to assess functional independence in MPS (Lee et al., 2019).

The walk test is a clinical tool to measure endurance as well as the severity of cardiac and lung involvement and is an indicator of functional status and aerobic capacity (Harmatz et al., 2005). Patients with severe MPS symptoms display impaired walking ability and reduced walking distance before the age of 10 (Swiedler et al., 2005).Studies investigating aerobic capacity in relation to ERT have been conducted in MPS I, II and VI patients older than 5 years of age. There are a limited number of studies examining aerobic capacity in children aged 5 years or younger (Muenzer, 2014). Since our study included children with a mean age of 5.58 years, it adds valuable data to the relevant literature.

The children ERT-treated group performed better on 6-minute walk and timed up and go tests compared to children not treated with ERT but this could not be demonstrated statistically. MPS types generally differ in that respect. Early diagnosis and initiation of ERT were shown to affect the aerobic capacity to a greater extent in MPS type VI (Muenzer, 2014). Consistently, we observed greater aerobic capacity in children with MPS type VI who were receiving ERT than in their counterparts not receiving ERT. However, there are controversial data in the literature for the impact of ERT on aerobic capacity in individuals diagnosed with MPS type IV (Do Cao et al., 2016). This was also the case in our study and ERT use did not change aerobic capacity of the children with MPS type IV. Thus, we believe that while early initiation of ERT may generally have a beneficial effect on functional independence in daily activities such as self-care, eating, and bowel and bladder control, it has no effect on aerobic capacity and physical endurance.

Age is associated with reduced quality of life irrespective of MPS type and ERT use (Swiedler et al., 2005). In a study by Needham et al. found that MPS Type II patients had significantly lower PedsQL scores compared to patients with other progressive illnesses, suggesting that Type II disease may have an adverse effect on quality of life. The authors of that study reported that although ERT

slows the disease progression, it has no effect on quality of life and that long-term follow-up is needed (Needham et al., 2015). In the current study, while we had no children with MPS type II, we consider that ERT alone is not sufficient to slow disease progression in children with other MPS types.

Balance problems mostly occur in neurodegenerative diseases. Ataxia is the most common form of neurodegenerative disease and the involvement of cerebellar structures causes a reduction in trunk control. In terms of functional reach, ERT did not have an effect on trunk control in sitting position in our subjects. With MPS types affecting primarily the musculoskeletal system represented in our study, this may indicate that proprioceptive sense is affected similarly and that, ERT has no effect on this sensation. Mucopolysaccharidosis type II is associated with more severe neurologic deficits and cranial GAG deposits are seen. From this point of view, MPS type II patients may experience more balance problems than patients with other MPS types. Therefore, the absence of any MPS type II patients in our study may not have contributed to the lack of a difference in balance as assessed by functional reach.

It is known that mothers of disabled children have higher levels of anxiety and depression and reduced quality of life (Bumin et al., 2008). Mitochondrial diseases are multi systemic, chronic conditions with a high incidence of disability and have a profound psychosocial impact on both affected individuals and their families (Kim et al., 2010). Moreover, lack of adequate knowledge on the disease may increase the depression and anxiety levels of caregivers (Guarany et al., 2015). In the present study, caregivers of children with MPS were found to suffer from moderate anxiety and depression. In a study investigating depression in caregivers of children with cerebral palsy (CP) and healthy children using the BDI, the BDI scores were 18.30 for the caregivers of children with CP and 7.34 for the caregivers of healthy children. In the same study, the BAI scores were 10.75 for the caregivers of children with CP and 9.78 for the caregivers of healthy children (Ones et al., 2005). In our study, the caregivers of children with MPS had a BDI score of 20.07 points and The BAI score of the caregivers of children with MPS was 19.07. The BDI and BAI scores of the caregivers obtained in the current study are higher than those of caregivers of CP patients. Similarly, depression and anxiety levels of the caregivers of patients with Duchenne muscular dystrophy were the same as those of the caregivers of patients with MPS (Çakaloz et al., 2005). This may be related to progressive, systemic effects of MPS and poor knowledge about this rare disease among caregivers. While ERT slows the disease progression in MPS, supporting affected children with conservative approaches such as a regular physiotherapy and rehabilitation program may improve their functional independence and possibly reduce anxiety and depression in caregivers. The feedback from caregivers in our study who reported that their children have never participated in a physiotherapy and rehabilitation program on a regular basis apart from receiving medical treatment clearly indicates the need for such intervention. Lack of rehabilitation for these children may be related to socio-cultural challenges, low parental education level as well as family economic hardship and we believe that this should be investigated in rare diseases.

5. Conclusion

ERT did not change aerobic capacity and quality of children with MPS but increased their level of functional independence. Multisystem involvement in MPS children may affect anxiety and depression levels of their caregivers but ERT does not seem to have any effect on this psychosocial aspect.

Limitations

Our sample size was small, which can be regarded as a limitation. Studies involving larger patient populations are warranted. However, it should be kept in mind that MPS is a rare disease. Some of the children may have developed the disease at an early age and their families may have been burdened by the disease earlier than others, which could have affected their BDI and BAI scores. Studies are needed to follow caregivers of children with MPS over a long term with respect to depression and anxiety.

Author Contributions

All authors have equal contribution and authors reviewed and approved the manuscript.

Conflict of Interest

The author declared that there is no conflict of interest.

Ethical Approval/Informed Consent

Parents included in the study were explained about the study in accordance with the Declaration of Helsinki. Written informed consent was obtained from the children and their parents, stating that their participation was voluntary. Ethics approval for the study was granted by the Institutional Review Board of Hasan Kalyoncu University (Approval No.: 2020/117).

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