Available online at www.medicinescience.org

ORIGINAL ARTICLE

Medicine Science International Medical Journal

Medicine Science 2022;11(3):1184-9

Evaluation of endocrine functions before and after enzyme replacement therapy in children with mucopolysaccharidosis

Ismail Dundar[1], Nurdan Ciftci[1], Aysehan Akinci[1], Emine Camtosun[1], Leman Kayas[1], Ahmet Sigirci[2], Fatma Hilal Yagin[3]

[1]Inonu University Faculty of Medicine, Department of Pediatric Endocrinology, Malatya, Turkey
[2]Inonu University Faculty of Medicine, Department of Radiology, Malatya, Turkey
[3]Inonu University Faculty of Medicine, Department of Biostatistics and Medical Informatics, Malatya, Turkey

Received 04 March 2022; Accepted 15 June 2022
Available online 08.08.2022 with doi: 10.5455/medscience.2022.03.053

Abstract

There is a scarcity of data concerning endocrine function and the effects of enzyme replacement therapy (ERT) on growth and other endocrine functions in patients with mucopolysaccharidosis (MPS). This study retrospectively evaluated height increase, bone mineral density (BMD), and other endocrine functions in MPS patients who received ERT for at least two years in our clinic. The clinical findings, hormonal analysis (TSH, fT4, ACTH, cortisol, FSH, LH, testosterone, estradiol, prolactin, GH, IGF-1, IGFBP-3), and BMD measurements of 10 MPS patients, aged 0-18 years, before and after ERT were recorded and compared retrospectively. Four patients were MPS Type-2, five were MPS Type-4, and one was MPS Type-6. Nine of the patients were male, and one was female. The mean treatment onset age was 7.6 years. The mean ± standard deviation of the patients' height SDS was -4.61±3.01 before treatment and -5.65±2.42 after treatment. While the mean BMD Z-score of the patients was -2.33±1.77 before treatment, it was -0.94±1.52 after treatment. Apart from growth retardation (one of the most prominent disease features), no severe dysfunction was detected in other endocrine organs in our patients with MPS. Severe short stature was evident at the time of diagnosis in MPS patients, and their height SDS worsened, despite ERT. However, osteoporotic BMD Z-scores at diagnosis improved after ERT. No serious dysfunction was seen in other endocrine organs.

Keywords: Mucopolysaccharidosis, enzyme replacement therapies, endocrine function, growth, bone mineral density

Introduction

Mucopolysaccharidoses (MPS) are a group of metabolic diseases that develop due to a deficiency of enzymes responsible for the metabolism of glycosaminoglycans (GAG; galactose, heparan sulfate, dermatan sulfate, keratan sulfate, hyaluronan) in lysosomes, resulting in GAG accumulation in lysosomes and tissues, and organ dysfunction [1]. As a chronic, progressive, multisystemic disease, seven types of MPS have been described to date including MPS I (H, S), MPS II, MPS III (A, B, C, D), MPS IV (A, B), MPS VI, MPS VII, and MPS IX. MPS II is inherited in an X-linked fashion, while the others are inherited autosomal recessively [2]. MPS I [MPS1H (Hurler), MPS1S (Scheie)] develops due to alpha-L-iduronidase enzyme deficiency, while MPS II (Hunter) occurs as a result of iduronate 2-sulfatase deficiency. Heparan sulfate is decreased in MPS III (Sanfilippo), while galactose-6-sulfate sulfatase and β-galactosidase enzyme activities are decreased in MPS IV (Morquio). MPS VI, known as Maroteaux-Lamy syndrome, occurs due to N-acetyl galactosamine 4-sulfatase (arylsulfatase B) enzyme deficiency. In addition, there is beta-D-glucuronidase enzyme deficiency in MPS VII (Sly syndrome) and hyaluronidase enzyme deficiency in type IX (Natowicz syndrome) [3-5].

In patients with MPS, structural and functional disorders occur due to the accumulation of GAG in different organs, which become evident with age and from birth. In all MPS types retardation in growth and development between the ages of 1.5-6 years [6-10], and complete or partial losses in pubertal growth spurt are observed [7-9,11,12]. Clinical findings seen in MPS include developmental delay, skeletal deformities, dysostosis multiplex, joint contractures, blurred cornea, hearing loss, hepatosplenomegaly, coarse face, adenoid hypertrophy, inguinal hernia, heart and respiratory failure, behavioral disorders, and mental retardation. Growth retardation

***Corresponding Author:** Ismail Dundar, Inonu University Faculty of Medicine, Department of Pediatric Endocrinology, Malatya, Turkey
E-mail: ismail_dundar@yahoo.com

and skeletal deformities are prominent findings in MPS IVA, while mental retardation, hearing loss, and kyphosis are more common in MPS IH and MPS II. Unlike other MPS types, the Sanfilippo variant causes behavioral disorders, hyperactivity, and developmental delay with speech disorder prominent. In the recently described MPS IX, common findings similar to rheumatoid arthritis are evident [1]. GAG, which cannot be metabolized in MPS, can accumulate in endocrine glands such as the pituitary, adrenal, and thyroid, causing endocrinological disorders. With the recently developed stem cell transplantation and enzyme replacement therapy (ERT), it is possible to stop the progression of the findings and partially improve the function of impaired organs [3].

There is insufficient data on endocrine function in MPS and the effects of ERT on growth and other endocrine functions. Therefore, this retrospective study evaluated height increase, BMD, and other endocrine functions, assessed by hormone measurements in MPS patients who received ERT for at least two years during the period 2012 to 2020.

Materials and Methods

Study population

The study included MPS patients who received ERT for more than two years in our clinic, during the period 2012 to 2020. Before and after ERT, clinical findings, auxological evaluation including height, weight, and body mass index (BMI), hormone analyzes (thyroid function, adrenal function, gonadal function and growth axis), and BMD measurements were analyzed retrospectively.

Anthropometric measurements

Anthropometric assessment was performed in the morning, following an overnight fast. The heights of the cases were measured with a wall-mounted stadiometer (SECA, Hamburg, Germany) while standing in a neutral position, heels together and no shoes. Weight measurement was performed via BMI SECA scale (with sensitivity to 0.1kg). Body mass index = body weight (kg)/height^2 (m^2) was calculated using the formula.

Laboratory measurements

Hormone analyzes included measurement of thyroid stimulating hormone (TSH), free thyroxine (fT4), adrenocorticotropic hormone (ACTH), cortisol, follicle stimulating hormone (FSH), luteinizing hormone (LH), testosterone, estradiol, prolactin, growth hormone (GH), insulin-like growth factor 1 (IGF-1), and IGF binding protein 3 (IGFBP-3). A growth hormone peak response of <10mcg/L with two different growth hormone stimulation tests (clonidine and L-dopa) was evaluated as growth hormone deficiency (GHD) [13]. In a patient whose baseline ACTH and cortisol levels were low in the post-treatment evaluation, an ACTH stimulation test (1 mcg intravenous) was performed. Adrenal insufficiency was excluded when the peak serum cortisol level was higher than 18mcg/dL [14] after stimulation. Serum TSH, fT4, cortisol, prolactin, FSH, LH, estradiol, and testosterone levels were analyzed by electrochemical irradiance immunoassay using the Elecsys 2010 modular analytical E170 device (Roche Diagnostics, Indianapolis, IN, USA). Serum GH and ACTH levels were measured with the Roche Cobas 6000 and Roche Cobas e601 devices (Roche Diagnostics, Indianapolis, IN, USA) using an electrochemiluminescence method. IGF 1 and IGFBP-3 measurements were made using the Siemens Immulite 2000 device (Siemens Healthcare Diagnostics Inc., Deerfield, IL, USA) by chemiluminescence method.

DEXA measurements

BMD measurements were made with dual-energy X-ray absorptiometry (DEXA, HOLOGIC QDR 4500W, Bedford, MA, USA). Results were expressed as grams of bone mineral per square centimetre (g/cm^2). The mean values for Caucasians and T-score and Z-score calculations were automatically performed by the in-built software. The Z-score for children was calculated using the following formula: (Measured BMD)–(Own-age-group-BMD)/(Own-age-group-standard deviation). The results were converted into Z-scores adjusted for height and gender for Turkish children [15].

Ethical approval: Subjects were enrolled following approval of the study protocol by the medical ethics committee (Ethics Committee of the Inonu University, approval number: 2021/2064), and receipt of written informed consent from parents.

Statistical Analysis

First, the missing values (for the dexa parameter) were assigned according to the mean. The compliance of quantitative variables to normal distribution was checked with the Shapiro-Wilk test. Quantitative variables that satisfy the assumption of normal distribution were summarized with the mean (standard deviation) and the quantitative variables that do not provide this assumption were summarized with the median (minimum/maximum). In the statistical analysis, dependent groups t-test was used for comparison of pre-treatment and post-treatment measurements of the normally distributed variables, and the Wilcoxon test was used for comparison of pre-treatment and post-treatment measurements of the non-normally distributed variables. $p<0.05$ was considered statistically significant. SPSS [SPSS I. Statistics for Macintosh (Version 26.0) [Computer software]. Armonk, NY: IBM Corp. 2019.] programming languages were used for data analysis.

Results

The study included 10 MPS patients, aged between 1.5 and 18 years. Nine of the ten patients were male, and one was female. Four patients with MPS II were receiving idursulfase (elaprase), five patients with MPS IV were treated with elosulfase alfa (vimizim), and one patient with type VI was receiving galsulfase (naglazyme). The duration of patients receiving ERT ranged from 2.5 to 8 years. The auxological parameters of our patients before and after treatment are shown in Table I. The mean age at the onset of ERT treatment was 7.63±4.0 years. When the results of the dependent t-test are examined, there is a statistically significant difference between the pre-treatment and post-treatment measurements in terms of the Height SDS ($p=0.018$) and DEXA Z score ($p=0.017$) parameters (see Table II).

In Type II MPS patients the mean age of onset of therapy to ERT was 6.49±4.88 years and the height SDS of patients before ERT treatment was median (min/max) -1.865(-4.3/0.88) and median (min/max)-3.555(-5.5/-0.83) after treatment ($p=0.068$). While the mean BMI SDS of these patients was median (min/max) 0.425 (-0.67/1.71) and median (min/max) 0.425(-1.23/2.5) after treatment ($p=0.715$).

Similarly, in Type IV MPS patients the mean age of onset of ERT was 7.06±1.7 years and the mean height SDS before ERT

treatment was median (min/max)-5.7(-6.7/-5.3) and median (min/max)-6.7(-8.59/-6.5) after treatment (p=0.078). While the mean BMI SDS of these patients was median (min/max) 1.53(0.57/1.9) and 0.6(0.03/1.26) after treatment (p=0.043).

The age at onset of treatment for the type VI MPS patient was 15 years. While the height SDS in this patient was -9.2 before ERT treatment, it had improved to -7.6 after treatment. The BMI SDS of this patient did not change before and after treatment and remained at 0.98.

Pre-treatment serum TSH, fT4, ACTH, cortisol, FSH, LH, testosterone, estradiol, prolactin, GH, IGF-1, and IGFBP-3 levels of the patients were within normal limits. After treatment, a patient with low baseline ACTH and cortisol levels had a normal response to the intravenous ACTH stimulation test (post-test peak cortisol level: 25mcg/dL). Three of the patients receiving treatment (1 patient type II, 2 patients type IV) had an inadequate response to growth hormone stimulation test (<10mcg/dL) and were diagnosed with growth hormone deficiency (GHD). After an average of 4.95 years of ERT treatment in all our patients, TSH, fT4, FSH, LH, estradiol-testosterone, and prolactin levels were normal (Table III).

The median (range) DEXA z-score of the ten patients in whom data was available (type II n=4; type IV n=5; type VI n=1) was-2.33±1.77 pre-treatment and -0.94±1.52 post-treatment (p=0.017). In the type II patients mean BMD z-score was median (min/max)-0,89(-2.09/1.5) pre-treatment and median (min/max)-0.22 (-1.8/2.2) post-treatment (p=0.465). Similarly, in the type IV patients median (range) BMD z-score was median (min/max)-2,6 (-4.3/-2.09) pre- treatment and median (min/max)-2.3(-2.8/-0.02) post-treatment (p=0.043). The BMD z-score of the type VI patient was-3.4 pre-treatment and-0.5 post-treatment.

Table 1. Treatment initiation age, duration of treatment, DEXA Z-score, BMI SDS, and height SDS follow-up profile of our cases

Patient (Gender)	MPS Type	Treatment Start Age, years	Treatment, and duratıon (years)	Before and after treatment	Height SDS	BMI SDS	Bone age(year)	DEXA *Z score
P1 (M)	Type 2	1.3	Elaprase (idursulfase), 4	Before treatment	0.88	1.71	1	-0.3
				After treatment	-0.83	2.5	3.5	-1.8
P2 (M)	Type 2	3.3	Elaprase (idursulfase), 8	Before treatment	-0.33	-0.02	3	-
				After treatment	-2.21	-0.59	9	0.14
P3 (M)	Type 2	11.2	Elaprase (idursulfase), 8	Before treatment	-4.3	-0.67	6	-1.48
				After treatment	-4.9	-1.44	15	-0.59
P4 (M)	Type 2	10.0	Elaprase (idursulfase), 8	Before treatment	-3.4	0.87	6	1.5
				After treatment	-5.5	-1.23	Epiphyses closed	2.2
P5 (M)	Type 4A	9.8	Vimizim (elosulfase alfa), 4	Before treatment	-6.7	0.57	3.5	-3.7
				After treatment	-8.59	0.15	6.4	-2.8
P6 (M)	Type 4A	6.4	Vimizim (elosulfase alfa), 3	Before treatment	-5.4	1.9	3.5	-4.3
				After treatment	-6.7	1.26	7	-2.5
P7 (M)	Type 4A	7.5	Vimizim (elosulfase alfa), 2.5	Before treatment	-6,6	1.61	4.5	-2.5
				After treatment	-6.5	0.03	6	-1.25
P8 (M)	Type 4A	5.7	Vimizim (elosulfase alfa), 4	Before treatment	-5.7	1.53	5	-
				After treatment	-7.0	0.98	7	-0.02
P9 (M)	Type 4A	5.8	Vimizim (elosulfase alfa), 4	Before treatment	-5.3	1.1	4	-2.6
				After treatment	-6.7	0.6	6	-2.3
P10 (F)	Type 6	15.0	Naglazyme (galsulfase), 3	Before treatment	-9.2	0.98	-	-3.4
				After treatment	-7.6	0.98	Epiphyses closed	-0.5

P, Patient; **F,** Female; **M,** Male; **MPS,** Mucopolysaccharidosis; **DEXA,** *Dual-energy X-ray absorptiometry; **BMI,** Body Mass Index; **SDS,** standard deviation score

Table 2. Height SDS, BMI SDS and DEXA Z score of all patients before and after treatment

Variable	Pre-treatment	Post-treatment	p value
	Mean ± SD	Mean ± SD	
Height SDS	-4.605±3.013	-5.653±2.423	0.018*
BMI SDS	0.958±0.816	0.612±1.071	0.373*
DEXA Z score	-2.33±1.77	-0.94±1.52	0.017*

DEXA, Dual-energy X ray absorptiometry; **BMI,** Body Mass Index; **SDS,** standard deviation score. *: Dependent t test

Table 3. Hormone concentrations before and after enzyme replacement therapy in MPS patients

Patient (Gender)	Time point	fT4 TSH	ACTH Cortisol	FSH LH	Prolactin	Growth Hormone	IGF-1SDS	IGFBP-3SDS
P1 (M)	Before treatment	1.06	-	-				
		1.35						
	After treatment	1.04	11.6	2.22	15.5	2.4	1.89	-0.18
		1.29	11.1	0.13				
P2(M)	Before treatment	1.74	60.4	0.5	7.03	1.09	-2.06	-0.21
		2.3	17.5	0.11				
	After treatment	1.31	12.7	2.34	2.05	6.04	-1.02	-1.44
		1.2	6.96	<0.01				
P3(M)	Before treatment	1.04	29.4	0.627	8.2	2.98	-2	-1.93
		2.98	10.3	0.04				
	After treatment	1.02	21.7	2.54	2.98	4.94	-1.99	-0.27
		1.06	7.79	0.93				
P4(M)	Before treatment	102	20.8	1.94	5.2	3.49	-2.97	-1.6
		1.06	6.48	0.138				
	After treatment	1.15	15.8	7.23	4.51	6.1	-1.48	0.32
		1.2	6.25	2.27				
P5(M)	Before treatment	123	11.4	0.53	8.2	1.01	-2.45	-1.79
		1.52	6.91	<0.01				
	After treatment	1.11	16.9	2.29	6	1.4	-0.26	1.15
		2.78	9.5	1.79				
P6(M)	Before treatment	131	80.5	-	-	4.56	-0.75	-
		1.58	5.38					
	After treatment	1.49	27.7	0.54	9.33	5.33	-0.33	0.22
		1.2	8.38	<0.01				
P7(M)	Before treatment	1.1	48		-	-	-	-
		1.62	18.9					
	After treatment	1.56	21.4	0.26	8.64	2.06	-1.48	1.37
		2.98	12.45	<0.01				
P8(M)	Before treatment	1.29	12.2	0.99	8.98	1.4	-2.92	-1.06
		1.95	6.41	0.33				
	After treatment	1.54	*2.53	0.94	4.63	2.31	2.11	2.58
		0.26	1.37	<0.01				
P9(M)	Before treatment	1.44	-		-	-	-	-
		1.18						
	After treatment	1.24	72.4	2.13	15.8	0.84	0.03	2.18
		1.41	22.5	0.12				
P10(M)	Before treatment	1.23	10	0.8	9.68	0.62	-2.85	-3.1
		1.87	5.88	<0.01				
	After treatment	1.21	36.7	2.99	17.4	2.98	-1.7	-0.11
		4.72	13.68	3.7				

P, Patient; **F,** Female; **M,** Male; **fT4**, Free Thyroxine; **TSH**, Thyroid-stimulating hormone; **ACTH,** Adrenocorticotropic hormone; **LH,** Luteinizing hormone; **FSH,** follicle-stimulating hormone; **IGF-1**, Insulin-like growth factor-1; **IGFBP-3,** Insulin-like growth factor binding protein-3. Normal range for FSH; Males, 1.7–12; Females, 1.5–12 IU/L, for LH; Males, <0.2–7, Females, 0.2–8 IU/L, for TSH; 0.33–6 mIU/mL, for fT4; 0.83–1.76 ng/dL, for ACTH;7.2-63.3 pg/mL, for Cortisol; 3.1-22.4 mcg/dL, for prolactin; 2.1–17.7 ng/mL, for GH; 0.09–6.29 ng/mL, *Low-dose ACTH stimulation test was performed on the patient, peak cortisol response was 25 mcg/dl.

Discussion

GAG deposition has been reported in the pituitary gland, exocrine and endocrine cells of the pancreas, adrenocortical cells, follicular epithelial cells of the thyroid, and gonads in MPS patients [3]. This may be one of the causes of growth retardation and other endocrine system disorders. The most clinically prominent stunted growth occurs in MPS type IVA, followed by MPS VI, MPS VII, and then MPS II; growth retardation is not the primary finding in MPS III [1]. Final stature is always shorter than healthy individuals in all forms of MPS [9]. The pathogenesis of short stature in MPS is not fully elucidated, but progressive deposition of GAG in cartilage and bone tissue has been implicated as the cause of skeletal deformities and short stature in these patients. Simonaro et al. reported that GAG storage causes apoptosis of cartilage cells, damage to the growth plate, and hyperplasia of synovial membranes, leading to disruption of the connective tissue structure [16]. The effect of ERT on long-term growth in patients with MPS has been investigated although results are contradictory. Some studies have shown that ERT has a positive impact on growth in patients with MPS type II [17] while others have reported no effect on growth [18]. Doherty et al. showed that the growth of 128 MPS type IV patients receiving ERT was not different from untreated patients [11]. Other studies have demonstrated that ERT has no significant effect on growth in patients with MPS type IV [19]. Although there are studies [8,20] showing the positive impact of ERT on growth in patients with MPS type VI, Lin et al. reported that patients with MPS type VI treated with ERT did not achieve a significant gain in height, and none of the patients reached the 3rd percentile in final height [21].

In our patients, severe short stature was present at diagnosis, and worsening of height SDS was observed, despite ERT. There was no significant increase in BMI SDS in any of our patients. This may suggest that the rapid progression in the natural process of the disease is slowed by ERT. The mean age of our patients at the start of ERT was 7.6 years, although this ranged widely from 1.3 to 15 years. This relatively late start of treatment may have skewed some of the growth change due to early compromise of the normal growth process. However, adequate treatment duration was not present in two type II cases in whom ERT was started before 5 years of age.

While serum basal growth hormone levels were high in three of our patients, serum basal IGF-1 (ng/ml) levels were low in five of our patients, and GHD was detected in three patients. This suggests, respectively, a GH receptor synthesis defect in the liver (which is expected in MPS), insufficiency of IGF-1 synthesis (the mediator of GH signaling), and development of GHD due to GAG accumulation in the pituitary. Cases that benefited from GH replacement have been reported in the literature. In the case series published by Cattoni et al., it was shown that there was a significant increase in the rate of growth with GH treatment, lasting 12-24 months, in MPS patients, of whom two had MPS IH [Hurler/Scheie syndrome], one had MPS IV, and one had MPS VI nd all of whom had developed GHD [22]. More evidence is needed on the efficacy of GH treatment in MPS patients with GHD. We regularly evaluate our patients in terms of GD treatment.

In patients with MPS, there is an increased risk of poor bone mineralization due to decreased physical activity resulting from malnutrition, gait disturbance, pain, poor general condition, or exercise intolerance [23]. Our study observed a significant improvement in the DEXA BMD z-score values of our patients after ERT compared to the pre-ERT baseline. Although it has been reported that bone growth and mineralization are affected by GAG deposition in animal models of MPS [24], few studies have evaluated BMD in patients with MPS [23,25]. In the survey conducted by Lin et al., it was shown that there was a significant improvement in BMD after treatment in eight patients with MPS (types II and VI) who received ERT treatment for between 1 and 7.4 years [26]. The improvement in BMD with ERT in MPS patients can probably be explained by multiple mechanisms, such as decreased GAG deposition in the bones, increased muscle strength and endurance, and improved pulmonary function and mobility [21,27].

The sex steroid profile and pubertal status of all of our patients were appropriate for their age. The study of Celeste et al. found puberty delay in 10 of 56 MPS VI patients who received ERT and reported that they had puberty progression with two years of ERT treatment, and six of them completed puberty [28]. In the case report published by Linxin et al., the sex steroids of a 17-year-old MPS type IV patient were reported as normal [28].

There was no abnormality in thyroid function tests in any of our patients. This finding was consistent with studies in the literature [8,28]. In another study conducted in 2011, in which 78 patients were followed up with MPS IVa, and 50 healthy controls were compared, no significant difference was reported in TSH levels [29]. In a case report published in 2019, TSH and fT4 values of MPS type II patients were reported to be within normal limits [30].

In our study, the basal ACTH and cortisol values of the patients before and after ERT were within normal limits. In addition, the response of Patient 8 (MPS type IV) to the ACTH stimulation test, whose baseline ACTH and cortisol levels were low after treatment, was evaluated as normal. Linxin et al. found low baseline ACTH and cortisol levels in a 17-year-old MPS IV patient in their case report. They stated that adrenocortical insufficiency may be associated with compression-related organ dysfunction caused by skeletal deformities in the patient with normal pituitary MRI and adrenal imaging [28]. Some limitations of the study are that (1) the number of cases is low; (2) there was no control group; (3) different age at onset of treatment; (4) wide age range; non-homogenous patient profile.

Conclusion

Apart from growth retardation, which is one of the most prominent features of MPS, no severe dysfunction was detected in other endocrine organs in our patients with MPS. It was observed that the height SDS of our patients did not improve with ERT. On the contrary, their height SDS worsened with age. As previously reported, the effect of ERT on height gain is limited. However, it should be kept in mind that, in addition to the known mechanisms of growth retardation in patients with MPS, GHD may occur despite ERT and was present in 30% of our patients. Although there is not enough data on the efficacy of GH treatment in MPS patients with GH deficiency, normal growth can be achieved with ERT, started at a very early age, together with effective metabolic control and GH treatment. It was observed that the decreased BMD of our patients improved with ERT. In conclusion, patients with

MPS should be followed up in terms of endocrine problems. It is predicted that good metabolic control with ERT treatment starting at an early age will be beneficial in preventing complications.

Conflict of interests
The authors declare that there is no conflict of interest in the study.

Financial Disclosure
The authors declare that they have received no financial support for the study.

Ethical approval
Subjects were enrolled following approval of the study protocol by the medical ethics committee (Ethics Committee of the Inonu University, approval number: 2021/2064), and receipt of written informed consent from parents.

References

1. Neufeld EF, Muenzer J. The mucopolysaccharidoses. In: Scriver CR, Beaudet AL, Sly WS, Valle D, eds. The metabolic & molecular bases of inherited disease. 8th ed. Vol. 3. New York: McGraw-Hill. 2001:3421-52.

2. Muenzer J. Overview of the mucopolysaccharidoses. Rheumatology (Oxford). 2011;50:5:4-12.

3. Polgreen LE, Miller BS. Growth patterns and the use of growth hormone in the mucopolysaccharidoses. J Pediatr Rehabil Med. 2010;3:25-38

4. Jezela-Stanek A, Różdżyńska-Świątkowska A, Kulpanovich A, et al. Novel data on growth phenotype and causative genotypes in 29 patients with Morquio (Morquio-Brailsford) syndrome from Central-Eastern Europe. J Appl Genet. 2019;60:163-74.

5. Suarez-Guerrero JL, Gómez Higuera PJ, Arias Flórez JS, Contreras-García GA. Mucopolisacaridosis: características clínicas, diagnóstico y de manejo [Mucopolysaccharidosis: clinical features, diagnosis and management]. Rev Chil Pediatr. 2016;87:295-304.

6. Melbouci M, Mason RW, Suzuki Y, et al. Growth impairment in Mucopolysaccharidoses. Mol Genet Metab. 2018;124:1–10.

7. Parini R, Jones SA, Harmatz PR, et al. The natural history of growth in patients with Hunter syndrome: Data from the Hunter Outcome Survey (HOS). Mol Genet Metab. 2016;117:438-46.

8. Decker C, Yu ZF, Giugliani R, et al. Enzyme replacement therapy for mucopolysaccharidosis VI: Growth and pubertal development in patients treated with recombinant human N-acetylgalactosamine 4-sulfatase. J Pediatr Rehabil Med. 2010;3:89-100.

9. Muschol NM, Pape D, Kossow K, et al. Growth charts for patients with Sanfilippo syndrome (Mucopolysaccharidosis type III). Orphanet J Rare Dis. 2019;14:93.

10. Harmatz P, Mengel KE, Giugliani R, et al. The morquio A clinical assessment program: baseline results illustrating progressive, multisystemic clinical impairments in Morquio A subjects. Mol Genet Metab. 2013;109:54-61.

11. Doherty C, Stapleton M, Piechnik M, et al. Effect of enzyme replacement therapy on the growth of patients with Morquio A J Hum Genet. 2019;64:625–35.

12. Rozdzynska A, Tylki-Szymanska A, Jurecka A, Cieslik J. Growth pattern and growth prediction of body height in children with mucopolysaccharidosis type II. Acta Paediatr. 2011;100:456-60.

13. Chiara Guzzetti, Anastasia Ibba, Sabrina Pilia, et al. Cut-off limits of the peak GH response to stimulation tests for the diagnosis of GH deficiency in children and adolescents: study in patients with organic GHD. Eur J Endocrinol. 2016;175:41-7.

14. Forest MG. Adrenal Function Tests. In: Ranke MB, ed. Diagnostics of endocrine function in children and adolescents. Basel: Karger Inc. 2003;372-426.

15. Damla Goksen, Sukran Darcan, Mahmut Coker, Timur Kose. Bone mineral density of healthy Turkish children and adolescents. J Clin Densitom. 2006;9:84-90.

16. Simonaro CM, D'Angelo M, He X, et al. Mechanism of glycosaminoglycan-mediated bone and joint disease: implications for the mucopolysaccharidoses and other connective tissue diseases. Am J Pathol. 2008;172:112-22.

17. Jones SA, Parini R, Harmatz P, et al, The effect of idursulfase on growth in patients with Hunter syndrome: data from the Hunter Outcome Survey (HOS). Mol Genet Metab. 2013;109:41-8.

18. Parini R, Rigoldi M, Tedesco L, et al. Enzymatic replacement therapy for Hunter disease: Up to 9 years experience with 17 patients. Mol Genet Metab Rep 2015;3:65–74.

19. Sawamoto K, Álvarez González JV, Piechnik M, et al. Mucopolysaccharidosis IVA: Diagnosis, Treatment, and Management. Int J Mol Sci. 2020;21:1517.

20. Giugliani R, Lampe C, Guffon N, et al. Natural history and galsulfase treatment in mucopolysaccharidosis VI (MPS VI, Maroteaux-Lamy syndrome) 10-year follow-up of patients who previously participated in an MPS VI Survey Study. Am J Med Genet A. 2014;164:1953–64.

21. Lin HY, Chen MR, Chuang CK, et al. Enzyme replacement therapy for mucopolysaccharidosis VI-experience in Taiwan. J Inherit Metab Dis. 2011;34:241.

22. Cattoni A, Motta S, Masera N, et al. The use of recombinant human growth hormone in patients with Mucopolysaccharidoses and growth hormone deficiency: a case series. Ital J Pediatr. 2019;45:93.

23. Fung EB, Johnson JA, Madden J, et al. Bone density assessment in patients with mucopolysaccharidosis: A preliminary report from patients with MPS II and VI. J Pediatr Rehabil Med. 2010;3:13.

24. Rowan DJ, Tomatsu S, Grubb JH, et al. Assessment of bone dysplasia by micro-CT and glycosaminoglycan levels in mouse models for mucopolysaccharidosis type I, IIIA, IVA, and VII. J Inherit Metab Dis. 2013;36:235–46.

25. Rigante D, Caradonna P. Secondary skeletal involvement in Sanfilippo syndrome. QJM. 2004;97:205-9.

26. Lin HY, Shih SC, Chuang CK, Chen MR, Niu DM, Lin SP. Assessment of bone mineral density by dual energy x-ray absorptiometry in patients with mucopolysaccharidoses. Orphanet J Rare Dis. 2013;8:71.

27. Lin SP, Shih SC, Chuang CK, et al. Characterization of pulmonary function impairments in patients with mucopolysaccharidoses-changes with age and treatment. Pediatr Pulmonol. 2013;49:277-84.

28. Xu L, Ren Y, Yin J, et al. Analysis of endocrine hormone metabolism level in a Chinese patient with mucopolysaccharidosis IVA: A case report. Medicine (Baltimore). 2018;97:e12393.

29. Martell L, Lau K, Mei M, et al. Biomarker analysis of Morquio syndrome: identification of disease state and drug responsive markers. Orphanet J Rare Dis. 2011;6:84.

30. Semyachkina AN, Voskoboeva EY, Zakharova EY, et al. Case report: a rare case of Hunter syndrome (type II mucopolysaccharidosis) in a girl. BMC Med Genet. 2019;20:66.