Cellular and Molecular Biology
E-ISSN : 1165-158X / P-ISSN : 0145-5680
www.cellmolbiol.org

Clinical, endocrine and genetic spectrums of mucopolysaccharidoses type VI in Duhok city, Kurdistan region, Iraq

Azad A. Haleem *

Department of Pediatrics, University of Duhok, College of Medicine, Gre Sor, Duhok, Kurdistan, Iraq

ARTICLE INFO

Original paper

Article history:
Received: Mai28, 2022
Accepted: July 20, 2022
Published: July 31, 2022

Keywords:

Mucopolysaccharidoses type VI, lysosomal storage diseases, genetic mutation, prenatal screening

ABSTRACT

Mucopolysaccharidoses type VI is a rare disorder and establishing the diagnosis requires assays that are unavailable in a routine care setting. There is an increased risk of considerable diagnostic delay and missing patients due to incorrect diagnosis. The present study was conducted to determine the socio-demographic characteristics, clinical manifestations, and anthropometric parameters of patients with MPS type VI. Patients' enzyme levels and genetic profiles were also examined. The present study included a total of 16 patients who had been diagnosed as MPS type VI and were referred to Hivi Pediatric Hospital in Duhok, Kurdistan Region, Iraq, till the time period of March 2022. Diagnoses were made in all the patients by analyzing the enzyme level. Moreover, a genetic study was performed to confirm the diagnosis. From each of the patients, a blood sample was taken to determine the hematological parameters. Among the study participants, 9 were males and 7 were females. The mean age of the patients was 6.81±4.99 years and the age at diagnosis was 21.13±15.19 months. All of them presented with a course facial features, 75% had short stature, 87.5% had corneal clouding, 12.5% had glaucoma, 68.75% had poor vision, 18.75% of them had optic nerve disease, 56.25% had otitis media, 56.25% had poor hearing, 68.75% had a history of recurrent sinusitis, 50% had an enlarged tongue, and 75% had abnormal teeth. Approximately 56.25% of the patients presented with sleep apnea, 37.5% had obstructive and restrictive airway disease, none of the patients had cardiac arrhythmia, 37.5% had cardiomyopathy, 31.25% had abdominal hepatosplenomegaly, 81.25% had skeletal abnormalities, all of the patients had normal intelligence, 9 (56.25%) had a past medical history of other systemic illness and 7 (43.75%) had a past history of surgery. Out of the total number of patients, 13 patients had c.962T>C (p.(Leu321Pro)) mutation, one patient had c.585T>A (p.(ASP195Glu)) mutation, one patient had c.[585T>A];[753C>G] (Asp195 Glu];[Tyr251 Ter]), and one patient had c.{288C>A];[962T>C] (p.[Ser96Arg];[Leu321Pro]) mutations. Due to the rarity in prevalence, early detection of the said disorder is critical; early treatment may result in improved outcomes, which may have potential significance for newborn screening.

Doi: http://dx.doi.org/10.14715/cmb/2022.68.7.11

Introduction

Mucopolysaccharidosis type VI (MPS VI), also known as Maroteaux–Lamy syndrome, is known to be a rare autosomal recessive metabolic disorder characterized by lower to lack of activity of the lysosomal enzyme N-acetylgalactosamine 4-sulfatase (arylsulfatase B; ASB), which facilitates one of the stages in the degradation of glycosaminoglycans (GAGs) dermatan sulfate (DS) and chondroitin 4-sulfate (CS). This causes a gradual amassing of the said molecules in lysosomes and extracellular matrix, resulting in cell and tissue damage, which culminates to a sequence of multi-organ dysfunction and significant clinical symptoms (5).

Patients with the severe stage of the said disease usually have symptoms well before the age of two or three years old and have mobility issues by the age of ten and they usually survive into their second or third decade. Patients with delayed or slowly advancing disease often display complications in later stages of life, frequently not recognizing them until they are in their adolescent or even adult years. Most individuals with MPS VI may experience severe clinical symptoms at some stage, such as joint deterioration, heart valve disease, sleep apnea, pulmonary dysfunction decline or decreased endurance (12).

GAG concentrations in the urine can be used as a screening method for MPS diseases. Although a positive test strongly suggests the presence of an MPS, false-negative outcomes are prevalent (18). Enzyme activity studies using cultured fibroblasts, leukocytes, plasma, or serum are the standard method for diagnosing MPS disorders. When a sulphatase shortage is discovered, the function of another sulphatase should be evaluated to eliminate the possibility of numerous sulphatase inadequacies (19). Following a biochemical assessment, gene sequencing can be used to determine the mutation(s) involved. At-risk family members can be provided genetic counseling and genetic carrier analysis if the gene mutation(s) in the MPS patient are identified, allowing for more conscious family planning (20).

* Corresponding author. Email: azad.haleem@uod.ac

Patients with MPS require frequent examinations, supportive therapy, and the support of a diverse clinical team capable of dealing with a wide range of systemic problems. For MPS patients with extensive somatic involvement, the surgical load is generally quite high (21, 22). Patients need to be observed and managed at a facility that has expertise in treating patients with MPS because of the disorder's intricacy and scarcity.

The present study was conducted to determine the socio-demographic characteristics, clinical manifestations, and anthropometric parameters of patients with MPS type VI. Patients' enzyme levels and genetic profiles were also examined. Endocrine abnormalities were also studied from several perspectives.

Materials and Methods

The present study included a total of 16 patients who had been diagnosed as MPS type VI and were referred to Hivi Pediatric Hospital in Duhok, Kurdistan Region, Iraq, till the period of March 2022. Ethical approval for the study was obtained from the Health Ethics Committee of the local directorate of health. Diagnoses were made in all the patients by analyzing the enzyme level. Moreover, a genetic study was performed to confirm the diagnosis.

All patients' clinical features were determined, Anthropometric measures were measured; Height was measured without shoes using a portable stadiometer; weight was measured in light clothing using a digital Heine portable scale. The most current anthropometric data from CDC were used to establish percentiles. For diagnosis, tandem mass spectrometry using dried blood spot were used to determine enzyme level and genetic study by ARCHIMED life Laboratories, Vienna, Austria, Europe.

From each of the analyses, a blood sample was taken to determine the hematological parameters such as TSH, T3, T4. PTH, Vit D3, Serum Ca, Spo4, Alkaline phospatese, IGF, ACTH, and Serum cortisol.

Statistical analysis

Data were entered in a Microsoft excel sheet and analysed by SPSS version 21. Descriptive statistics were performed to find the mean and standard deviations and frequency (%). The continuous variables were presented as mean±SD with minimum and maximum values and categorical variables were presented as frequency (%).

Results

Demographic and clinical characteristics

Table 1 represents the demographic and clinical characteristics of the patients. The mean age of the patients was 6.81±4.99 years (min=3, max=22). The age at diagnosis was 21.13±15.19 months (min=0, max=48). The mean BMI was 18.89±2.47 kg/m2 (min=15.38, max=24.15). The mean bone age was 4.22±2.61 years (min=1.0, max=12.0). The mean size of the head was 51.56±2.66 (min=44, max=55) (Table 1).

Of the total participants, 9 (56.25%) were males and 7 (43.75%) were females. Nine (56.25%) patients had a family history of mucopolysaccharidosis type 6. Thirteen (81.25%) patients had a history of consanguineous marriage. All of them presented with a course facial features, 12 (75%) had short stature, 14 (87.5%) had corneal clouding, 2 (12.5%) had glaucoma, 11 (68.75%) had a poor vision, 3 (18.75%) of them had optic nerve disease, 9 (56.25%) had otitis media, 9 (56.25%) had poor hearing, 11 (68.75%) had a history of recurrent sinusitis, 8 (50%) had an enlarged tongue, and 12 (75%) had abnormal teeth. Nine (56.25%) of the patients presented with sleep apnea, 6 (37.5%) had obstructive and restrictive airway disease, 2 (12.5%) had a low pulmonary function, 10 (62.5%) had a history of recurrent pulmonary infections, none of the patients had cardiac arrhythmia, 6 (37.5%) had cardiomyopathy, none had pulmonary hypertension, 5 (31.25%) had abdominal hepatosplenomegaly, 12 (75%) had an umbilical and inguinal hernia, 13 (81.25%) had skeletal abnormalities (dysostosismultiplex), 11 (68.75%) had joint stiffness and contractures, 6 (37.5%) had hip dysplasia, none of the patients had cervical spinal cord compression, 5 (31.25%) had carpal tunnel syndrome, 1 (6.25%) of the patients had to communicate hydrocephalus, all of the patients had normal intelligence, 9 (56.25%) had a past medical history of other systemic illness and 7 (43.75%) had a past history of surgery (Table 1).

Genetic analysis

Out of the total number of patents, 13 patient had c.962T>C (p.(Leu321Pro)) mutation, one patient had c.585T>A (p.(ASP195Glu)) mutation, one patient had c.[585T>A];[753C>G] (Asp195 Glu];[Tyr251 Ter]), and one patient had c.{288C>A];[962T>C] (p.[Ser96Arg];[Leu321Pro]) mutations (Table 2).

Hormone profile

The mean THS, T3, and T4 levels were 2.43±1.33 (min=0.26, max=5.37), 2.61±0.59 (min=1.54, max=3.62), and 113.36±12.86 (min=90.12, max=132.90) respectively. The mean IGF level was 91.73±59.20 (min=7.4, max=222.7), the mean ACTH level was 32.53±17.17 (min=5.5, max=75.0), the mean cortisone level was 154.28±71.81 (min=13.5, max=299.0), the mean PTH level was 36.71±23.59 (min=16.75, max=108.2) (Table 3).

Liver and kidney function

The mean SGPT, SGOT, and ALPH levels were 16.84±4.82 (min=9.0, max=29), 30.00±9.03 (min=16, max=49), and 224.38±78.13 (min=129, max=456) respectively. The mean urea, creatinine, Na, K, and Cl were 24.88±5.16 (min=16, max=34), 0.50±0.08 (min=0.35, max=0.70), and 105.29±3.64 (min=96.8, max=110.0) respectively (Table 4).

Sugar profile, Vitamin D, Calcium, and Enzyme level

The mean RBS and HbA1C were 92.33±14.44 (min=68.1, max=114.0) and 4.84±0.55 (min=4.0, max=5.6) respectively. The mean vitamin D and calcium levels were 31.91±13.36 (min=12.20, max=69.82) and 9.91±0.45 (min=9.30, max=10.80) respectively. The mean enzyme level was 0.01±0.01 (min=0, max=0.40) (Table 5).

Table 6 represents other observed blood parameters.

Discussion

Mucopolysaccharidosis type VI (MPS VI) is an autosomal recessive metabolic condition in which the lyso-

Table 1. Demographic and clinical characteristics.

Age (years)		6.81±4.99 (min=3, max=22)
Age of diagnosis (months)		21.13±15.19 (min=0, max=48)
Gender (males/females)		9 (56.25%)/7 (43.75%)
Family history		9 (56.25%)
Consanguinity		13 (81.25%)
Height (cm)		89.94±7.73 (min=74, max=101)
Weight (Kg)		15.30±2.85 (min=10.6, max=20)
BMI (kg/m2)		18.89±2.47 (min=15.38, max=24.15)
Bone age (years)		4.22±2.61 (min=1, max=12)
System	**Manifestation**	
Appearance and general symptoms	**Macrocephaly**	51.56±2.66 (min=44, max=55)
	Coarse facial features	16 (100%)
	Short stature	12 (75%)
Eyes, Ears, Nose, Throat	**Corneal clouding**	14 (87.5%)
	Glaucoma	2 (12.5%)
	Weak vision	11 (68.75%)
	Optic nerve disease	3 (18.75%)
	Recurrent otitis media	9 (56.25%)
	Weak hearing	9 (56.25%)
	Recurrent sinusitis	11 (68.75%)
Mouth, teeth	**Enlarged tongue**	8 (50%)
	Abnormal teeth	12 (75%)
Airways, respiration	**Sleep apnea**	9 (56.25%)
	Obstructive and restrictive airway disease	6 (37.5%)
	Low pulmonary function	2 (12.5%)
	Recurrent pulmonary infections	10 (62.5%
Heart	**Cardiac arrhythmia**	0
	Cardiomyopathy	6 (37.5%)
	Pulmonary hypertension	0
Abdomen	**Abdomen Hepatosplenomegaly**	5 (31.25%)
	Umbilical and inguinal hernias	12 (75%)
Bones, Joints	**Skeletal abnormalities (dysostosismultiplex)**	13 (81.25%)
	Joint stiffness and contractures	11 (68.75%)
	Hip dysplasia	6 (37.5%)
Brain, nerves	**Cervical spinal cord compression**	0
	Carpal tunnel syndrome	5 (31.25%)
	Communicating hydrocephalus	1 (6.25%)
	Normal intelligence	16 (100%)
Past Hx	**PMHx**	9 (56.25%)
	PSHx	7 (43.75%)

The continuous variables were presented as mean±SD and minimum and maximum and categorical variables were presented as frequency (%).

Table 2. The mutations were observed in the 5q11-q13 region.

Patients	5q11-q13 (identified mutations)
1	c.962T>C (p.(Leu321Pro))
2	c.962T>C (p.(Leu321Pro))
3	c.962T>C (p.(Leu321Pro))
4	c.962T>C (p.(Leu321Pro))
5	c.[585T>A];[753C>G] (Asp195 Glu];[Tyr251 Ter])
6	c.{288C>A];[962T>C] (p.[Ser96Arg];[Leu321Pro])
7	c.962T>C (p.(Leu321Pro))
8	c.962T>C (p.(Leu321Pro))
9	c.962T>C (p.(Leu321Pro))
10	c.962T>C (p.(Leu321Pro))
11	c.962T>C (p.(Leu321Pro))
12	c.585T>A (p.(ASP195Glu))
13	c.962T>C (p.(Leu321Pro))
14	c.962T>C (p.(Leu321Pro))
15	c.962T>C (p.(Leu321Pro))
16	c.962T>C (p.(Leu321Pro))

Table 3. Hormone profile.

	Mean± SD	**Minimum**	**Maximum**
TSH	2.43±1.33	0.26	5.37
T3	2.61±0.59	1.54	3.62
T4	113.36±12.86	90.12	132.90
IGF	91.73±59.20	7.4	222.7
ACTH	32.53±17.17	5.5	75.0
Cortisone	154.28±71.81	13.5	299.0
PTH	36.71±23.59	16.7	108.2

The variables were presented as mean±SD and minimum and maximum.

Table 4. Liver and kidney function.

	Mean± SD	**Minimum**	**Maximum**
SGPT	16.84±4.82	9.0	29.0
SGOT	30.00±9.03	16	49
ALPH	224.38±78.13	129	456
UREA	24.88±5.16	16	34
CREAT	0.50±0.08	.35	.70
NA	140.11±3.29	136.3	147.5
K	4.62±0.33	4.00	5.37
CL	105.29±3.64	96.8	110.0
Ca	9.91±0.45	9.30	10.80

The variables were presented as mean±SD and minimum and maximum.

Table 5. Sugar profile, Vitamin D, Calcium, and Enzyme level.

	Mean± SD	**Minimum**	**Maximum**
Enzyme level	0.01±0.01	0.00	.04
HBA1C	4.84±0.55	4.0	5.6
RBS	92.33±14.44	68.1	114.0
Ca	9.91±0.45	9.30	10.80
Vit.D	31.91±13.36	12.20	69.82

The variables were presented as mean±SD and minimum and maximum.

Table 6. Other blood parameters.

Parameter	Mean±SD	Minimum	Maximum
HB	12.36±1.34	10.0	14.7
WBC	10.37±3.99	6.0	17.5
PLT	298.06±90.99	152	493

The variables were presented as mean±SD and minimum and maximum.

somal enzyme N-acetylgalactosamine 4-sulfatase has low to nonexistent activity which causes a gradual accumulation of these molecules in lysosomes and extracellular matrix which leads to a sequence of organ failure with severe clinical symptoms (1). Increased urine GAG concentrations are correlated with a fast-advancing form of the said disease, and manifestation varies as according to the age of initiation and rate of progression of the disease. However, a substantial number of ASB gene mutations have been found and are thought to be relevant for the presentation variability (11, 12). Multiple publications revealing ARSB gene variations, the leading cause of the said disorder, have been published majorly in Middle East countries (8, 9, 10).

The manifestations of the said disease are presented in Table 1. A plethora of clinical features are reported in the literature pertaining to Mucopolysaccharidoses type VI. Although clinical symptoms differ by MPS subgroup, coarse aspects, organomegaly, skeletal and joint anomalies, visual and hearing difficulties, and cardiorespiratory issues are all frequent in the said group of population (19). A significant dysfunction of the osteoarticular systems, with dysostosis multiplex, low height, and motor deficits, are the characteristic clinical symptoms (6). Furthermore, ophthalmic anomalies (beyond corneal clouding) and ENT (ear, nose, and throat) symptoms, as well as oro-dental anomalies, were reported often (7). These mentioned characteristics were particularly noticeable in MPS VI, which is characterized by hypoplastic condyles, malposition of unerupted teeth, extensive dental follicles, with an expansive bite in the majority of patients (3). Moreover, several symptoms common to MPSs in practice, such as organomegaly and cardio-respiratory deficits, were also prevalent in MPS VI (5). The buildup of dermatan sulphate within the heart valves causes impairments in cardiac valve anatomy and function in all patients with MPS VI (13). Hyperlipidemia as a prospective cardiovascular risk factor in these patients is little understood. Despite having a higher BMI, MPS problems are not linked to substantial hypercholesterolemia or diabetes mellitus (14). Approximately 81.25% of the enrolled patients presented with skeletal abnormalities. The probable reason may be GAG buildup in articular cartilage, which appears to increase inflammation and chondrocyte death (23, 24). MMPs are released as a result of accelerated chondrocyte death, which causes persistent degenerative joint disease (24). Furthermore, aberrant biomechanical stress resulting from the inherent skeletal abnormalities was thought to worsen joint illness (25). Although degenerative abnormalities in joints can emerge as a result of long-term inflammatory joint illness, primary degenerative joint disease is uncommon in children and only happens in geographically confined demographics such as South Africa, China and India (26, 27).

The mean enzyme level in the studied group of patients was found to be 0.01±0.01. ARSB levels can be used to diagnose MPS VI. ASB catalyzes the hydrolysis of the C4-sulfate ester linkage in N-acetylgalactosamine-4-sulfate residues at the non-reducing ends of dermatan and chondroitin sulfate in healthy individuals during lysosomal degradation (15). In MPS VI patients, ASB's potential to activate the mentioned process is diminished or abolished; hence a diminished level of the said enzyme was noted in the enrolled pool of patients. The hormone levels were noted to be altered in the observed cases. Abnormal enlargement of the liver (hepatomegaly) is common in MPS VI individuals. Rare circumstances of MPS disease have been documented to have endocrine anomalies in the hypothalamic-pituitary-growth hormone (GH)/insulin-like growth (IGF) factor axis, while GH has also been identified as normal in isolated cases (16).

It was observed that the majority of enrolled patients (13) had c.962T>C (p.(Leu321Pro)) mutation while others demonstrated c.585T>A (p.(ASP195Glu)) mutation, c.[585T>A];[753C>G] (Asp195 Glu];[Tyr251 Ter]), and one patient had c.{288C>A];[962T>C] (p.[Ser96Arg];[Leu321Pro]) mutations (Table 2). It is a reported fact that the most prevalent mutations for the said disorder are c.454C > T [p.(Arg152Trp)] and c.962T > C [p.(Leu321Pro)] (1). In a literature search conducted elsewhere, the second most prevalent allele observed was c.962T>C [p.(Leu321Pro)] (2). Subjects homozygous with p.(Leu321Pro) showed a variety of clinical symptoms, ranging from a traditional, quickly developing phenotype to a non-classical, gradually progressive phenotype (3, 4). Reported studies imply the fact that the said mutations vary according to ethnicity of the studied groups. In a published study report, Giraldo et al. discovered 14 distinct mutations in 14 Colombian MPS IV individuals, including the p.Gly302Arg mutation (28). Val358Met variant was described as a polymorphism in Spanish and Argentinian MPS VI patients by Garrido et al. (28). In the year 2017, Abbasi and coworkers discovered the c.274A > C (p.Thr92Pro) missense homozygote mutation in an Iranian pool of patient with MPS VI. Furthermore, they discovered a polymorphism (variation p.V358 M) in the enrolled patient (29). Another study had 18 MPS VI patients from six distinct, unrelated consanguineous families. They discovered a homozygous c.753C > G mutation in the ARSB gene in the majority of studied cases (30).

Prenatal diagnosis during the first or second trimester of pregnancy can discover possible cases in households with a previous record of one of MPS VI. The percentage of enzymatic activity in the cells determines the disorder's prognosis. Hematopoietic stem cell transplant (HSCT) and enzyme replacement therapy (ERT) are two therapeutic options for reinstating, at least partially, the decreased enzyme's function in MPS (17).

MPS VII is a disorder that begins before birth. In the lack of prenatal screening, the majority of cases manifest immediately at birth. As with so many diseases, early

detection is critical; early treatment may result in improved outcomes, which could have potential significance for newborn screening. This underscores the need for MPS VII illness awareness. Because MPS VII is so uncommon, drug research for it is difficult. If a neurological end point is necessary, approval may be more challenging; yet, there is a better likelihood of success because similar illnesses have been approved previously. Enzyme replacement therapy has facilitated a fundamental transformation in the landscape of treatment for mucopolysaccharidosis I, II, and VI in the last decade, alongside hematopoietic stem cell transplant (for particular conditions). It contributes to offering a greater comprehension of the disease's pathophysiology.

Acknowledgements
None

Conflict of Interests
None

References

1. D'Avanzo F, Zanetti A, De Filippis C, Tomanin R. Mucopolysaccharidosis Type VI, an Updated Overview of the Disease. Int J Mol Sci 2021; 22:13456. https://doi.org/10.3390/ijms222413456
2. Tomanin R, Karageorgos L, Zanetti A, Al-Sayed M, Bailey M, Miller N, et al. Mucopolysaccharidosis type VI (MPS VI) and molecular analysis: Review and classification of published variants in the ARSB gene. Hum mutat 2018; 39:1788–802. https://doi.org/10.1002/humu.23613
3. Kantaputra PN, Kayserili H, Guven Y, Kantaputra W, Balci MC, Tanpaiboon P et al. Clinical manifestations of 17 patients affected with mucopolysaccharidosis type VI and eight novel ARSB mutations. Am J Med Genet Part A. 2014; 164:1443-53.
4. Zanetti A, Önenli-Mungan N, Elcioglu N, Özbek MN, Kör D, Lenzini E et al. Molecular analysis of Turkish Maroteaux-Lamy patients and identification of one novel mutation in the arylsulfatase B (ARSB) gene. In JIMD Reports, Volume 14 2013; 1-9. Springer, Berlin, Heidelberg.
5. Harmatz PR, Shediac R. Mucopolysaccharidosis VI: Pathophysiology, diagnosis and treatment. Front Biosci Landmark 2017; 22:385–406. doi: 10.2741/4490
6. Nicolas-Jilwan M, AlSayed M. Mucopolysaccharidoses: Overview of neuroimaging manifestations. Pediatr Radiol 2018; 48:1503–20.
7. Ballıkaya E, Eymirli PS, Yıldız Y, Avcu N, Sivri HS, Uzamış-Tekçiçek M. Oral health status in patients with mucopolysaccharidoses. Turk J Pediatr 2018; 60:400–6.
8. Malekpour N, Vakili R, Hamzehloie T. Mutational analysis of ARSB gene in mucopolysaccharidosis type VI: Identification of three novel mutations in Iranian patients. Iran J Basic Med Sci 2018; 21:950–6. doi: 10.22038/IJBMS.2018.27742.6760.
9. Jafaryazdi R, Shams S, Isaian A, Setoodeh A, Teimourian S. Identification of eleven different mutations including six novel, in the arylsulfatase B gene in Iranian patients with mucopolysaccharidosis type VI. Mol Biol Rep 2019; 46:3417–26.
10. Aminzadeh M, Malekpour N, Ghandil P. Identification of arylsulfatase B gene mutations and clinical presentations of Iranian patients with Mucopolysaccharidosis VI. Gene 2019; 706:1–5.
11. Muenzer J. Overview of the mucopolysaccharidoses. Rheumatology 2011; 50:v4–12.
12. Swiedler SJ, Beck M, Bajbouj M, Giugliani R, Schwartz I, Harmatz P et al. Threshold effect of urinary glycosaminoglycans and the walk test as indicators of disease progression in a survey of subjects with Mucopolysaccharidosis VI (Maroteaux-Lamy syndrome). Am J Med Genet A 2005; 134A:144–50.
13. Valayannopoulos V, Nicely H, Harmatz P, Turbeville S. Mucopolysaccharidosis VI. Orphanet J Rare Dis. 2010; 5:1-20.
14. Jurecka A, Golda A, Opoka-Winiarska V, Piotrowska E, Tylki-Szymanska A. Mucopolysaccharidosis type VI (Maroteaux-Lamy syndrome) with a predominantly cardiac phenotype. Mol Genet Metab 2011; 104:695–9.
15. Stepien KM, Stewart FJ, Hendriksz CJ. The factors affecting lipid profile in adult patients with Mucopolysaccharidosis. Mol Genet Metab Rep 2017; 12:35-40. doi:10.1016/j.ymgmr.2017.05.006
16. Vairo F, Federhen A, Baldo G, Riegel M, Burin M, Leistner-Segal S et al. Diagnostic and treatment strategies in mucopolysaccharidosis VI. Appl Clin Genet 2015; 8:245–55.
17. Toledo SP, Costa VH, Fukui RR, Abelin N. Serum growth hormone levels in Hunter's syndrome. Rev Hosp Clin 1991; 46:9-13.
18. Pereira VG, Martins AM, Micheletti C, D'Almeida V. Mutational and oxidative stress analysis in patients with mucopolysaccharidosis type I undergoing enzyme replacement therapy. Clin Chim Acta 2008; 387:75–9.
19. Mahalingam K, Janani S, Priya S, Elango EM, Sundari RM. Diagnosis of mucopolysaccharidoses: how to avoid false positives and false negatives. Indian J Pediatr 2004; 71:29-32.
20. Hall CW, Liebaers I, Di Natale P, Neufeld EF. [46] Enzymic diagnosis of the genetic mucopolysaccharide storage disorders. Meth Enzymol 1978; 50:439-56.
21. Arn P, Wraith JE, Underhill L. Characterization of surgical procedures in patients with mucopolysaccharidosis type I: findings from the MPS I Registry. J Pediatr 2009; 154:859-64.
22. Mendelsohn NJ, Harmatz P, Bodamer O, Burton BK, Giugliani R, Jones SA et al. Importance of surgical history in diagnosing mucopolysaccharidosis type II (Hunter syndrome): data from the Hunter Outcome Survey. Genet Med 2010; 12:816-22.
23. Simonaro CM, D'Angelo M, Haskins ME, Schuchman EH. Joint and bone disease in mucopolysaccharidoses VI and VII: identification of new therapeutic targets and biomarkers using animal models. Pediatr Res 2005; 57:701-7.
24. Simonaro CM, D'Angelo M, He X, Eliyahu E, Shtraizent N, Haskins ME 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.
25. Wraith JE. The first 5 years of clinical experience with laronidase enzyme replacement therapy for mucopolysaccharidosis I. Expert Opin Pharmacother 2005; 6:489-506.
26. Agarwal SS, Phadke SR, Phadke RV, Das SK, Singh GK, Sharma JP et al. Handigodu disease: a radiological study. Skeletal Radiol 1994; 23:611-9.
27. Morishita K, Petty RE. Musculoskeletal manifestations of mucopolysaccharidoses. Rheumatology 2011; 50:v19-25.
28. Giraldo GA, Ayala-Ramírez P, Prieto JC, García-Robles R, Acosta JC. Molecular findings of Colombian patients with type VI mucopolysaccharidosis (Maroteaux–Lamy syndrome). Meta Gene. 2016;7:83-9.
29. Abbasi S, Noruzinia M, Bashti O, Ahmadvand M, Chaleshtori AR, Mahootipou L. Another novel missense mutation in ARSB gene in Iran. Acta Medica Iranica. 2017:585-90.
30. Al-Sannaa NA, Al-Abdulwahed HY, Al-Majed SI, Bouholaigah IH. The clinical and genetic spectrum of Maroteaux-Lamy syndrome (mucopolysaccharidosis VI) in the Eastern Province of

Saudi Arabia. Journal of Community Genetics. 2018;9:65-70.