The clinical and genetic Spectrum of Maroteaux-Lamy syndrome (Mucopolysaccharidosis VI) in the Eastern Province of Saudi Arabia

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Abstract Mucopolysaccharidosis (MPS VI) or Maroteaux-Lamy syndrome is an autosomal recessive lysosomal storage disease caused by deficiency of the enzyme *N*-acetylgalactosamine 4-sulfatase or arylsulfatase B. It is involved in the degradation of glycosaminoglycans and characterized by a wide spectrum of clinical and genetic heterogeneity. So far, more than 150 mutations have been reported in the ARSB gene. Most of these mutations are either novel, private, or compound heterozygous making phenotype–genotype correlation as well as population screening difficult. The aim of our study is to determine the genotypes and phenotypes of MPS VI among the Saudi population at the Eastern Province of Saudi Arabia. The clinical data of all the patients seen and diagnosed with MPS VI (Maroteaux-Lamy syndrome) at the main hospital from January 1, 1983, to December 31, 2016, were reviewed. A total of 18 patients from 6 unrelated consanguineous families (first-cousin parents) were diagnosed with MPS VI during the defined 33 years. All of the affected patients displayed the severe phenotype of MPS VI. Only one genotype (c.753C > Gp.Y251X) was identified among five of the studied families. All of those families were inhabitants of Al-Hofuf area, but they descended from different clans. A second genotype (c270_274del5bp pc.91Afs*34) was detected in a single family who had originated from Abha area (the southern-west region of the country). This report demonstrated the homogeneity for both phenotype and genotype of our studied patients with MPS VI. This may eventually make selective asymptomatic carrier test and newborn screening highly feasible in this region of country.

Introduction

Mucopolysaccharidosis (MPS VI), or Maroteaux-Lamy syndrome (MIM no. 253200), is an autosomal recessive lysosomal storage disease resulting from the deficiency of the enzyme *N*-acetylgalactosamine 4-sulfatase or arylsulfatase B (ASB). This enzyme is responsible for the hydrolysis of the sulfate group of the glycosaminoglycans dermatan sulfate and chondroitin sulfate. Deficiency or lack of this enzyme activity will lead to a progressive intracellular accumulation of the glycosaminoglycans resulting into an irreversible multiorgan dysfunction and premature mortality.

MPS VI is characterized by a wide spectrum of clinical manifestation as with all MPS that includes skeletal deformities (dysostosis multiplex) with stunted growth, coarse facial feature, corneal opacity, hepatosplenomegaly, cardiac abnormalities, and usually a normal cognitive function (Valayannopoulos et al. 2010). The severe phenotype may have onset at birth with a progressive severe skeletal deformities and mortality within the second decade of life. A slowly progressive phenotype has a later onset on life with mild skeletal deformities and a survival up to the fifth decade of life. Since the identification of the gene (ARSB), more than 150 mutations have been described. Most of these mutations are either novel, or private, or compound heterozygous making phenotype–genotype correlation difficult as well as population screening.

Until recently, supportive care and bone marrow transplantation were the only treatment available for MPS VI patients. Supportive care has been focused to optimize the general well-being, family support, and counseling. Bone marrow or hematopoietic stem transplantation has been done for a limited number of patients worldwide. A long-term follow-up study had documented the restoration of a normal enzyme activity with a good visceral improvement. However, skeletal

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abnormalities remained a major problem for these patients (Herskhovitz et al. 1999).

Naglazyme (galsulfase) was approved as an enzyme replacement therapy (ERT) for MPS VI in May 2005 and was considered a safe and effective treatment (Harmatz et al. 2006). Case series had shown a significant improvement of cardiovascular function and stabilization of visual acuity. However, treatment before development of the anticipated skeletal deformities is mandatory in order to prevent this complication. Therefore, an early detection and diagnosis with an immediate intervention are crucial for a better outcome.

Here, we report 18 Saudi Arab affected patients from 6 unrelated consanguineous families seen and diagnosed at Johns Hopkins Aramco Healthcare (JHAH) from January 1, 1983, to December 31, 2016. Five of these families are inhabitants of Al-Hofuf area at the Eastern part of the Saudi Arabia, and one family had originated from Abha (The south west part of the country). Five patients had received ERT, and one had received bone marrow transplantation from a full-matched heterozygous sibling. The clinical course and the outcome for this homogenous group of patients were described.

Method

JHAH provides a comprehensive free healthcare for the employees of the Saudi Arabian American Oil Company and their families. This is distributed between several local community hospitals and a tertiary medical center in Dhahran city.

The files of all the patients seen and diagnosed with MPS VI (Maroteaux-Lamy syndrome) at the main hospital from January 1, 1983, to December 31, 2016, were reviewed. The study was approved by the institutional review board.

The patients were suspected to have MPS because of the presence of typical clinical features, or history of previously affected family members. The diagnosis was confirmed by measuring enzyme activity on either cultured skin fibroblasts or leukocytes on the index cases. Those tests were conducted outside our medical facility, at Mayo Clinic Biochemical Lab, Rochester, Minnesota, USA, or Willink Biochemical Lab, Manchester, UK.

Genetic study was done on at least one of the affected children of each family followed by confirming the heterozygosity on the parents, excluding family 1 where all the affected children as well as the father were deceased before the genetic study had become available. Retrospectively, the mother was tested for the common identified genotype in this population.

Results

A total of 18 patients from 6 different unrelated consanguineous families (first-cousin parents) were diagnosed with MPS

VI during the defined 33 years with an average of 3 affected children per family. Five of those families were inhabitants of Al-Hofuf area where the largest oasis in the Eastern Province of Saudi Arabia is located. All the tested affected individuals from these families were found to be homozygous for a known pathogenic nonsense c.753C>Gp.Y251X mutation in the ARSB gene. Family 6 who had originated from the Abha area (the southwest of the country) with one affected child was found to be homozygous for a previously undescribed frameshift c270_274del5bp pc.91Afs*34 mutation (Table 1).

The phenotype was severe in all of the affected individuals with the p.Y251X homozygous genotype with an onset within the first year of life. All had severe skeletal deformities causing a stunted growth, in addition to the other commonly known systemic complications including chronic respiratory symptoms, corneal opacity with significant visual impairment, and umbilical hernia. However, the phenotype was a bit more favorable in the patient with the second identified genotype. Urine for glycosaminoglycans (GAGs) concentration was available only for 5 patients and ranged from 586.2 to 941.6 µg GAG/mg creatinine.

Cardiac involvement with a severe mitral valve insufficiency was the presenting feature of patient 16 at 3 months of age.

Seven patients were misdiagnosed clinically with Hurler syndrome (MPS I). The patient from family 5 was misdiagnosed with isolated craniosynostosis with an obstructive hydrocephaly. Subsequently at 2 years of age, this patient developed cardiomyopathy precipitated by a chest infection requiring mechanical ventilation for 2 weeks.

In addition to supportive medical care, different surgical procedures were required for our studied patients. Seven patients had adenoidectomy/tonsillectomy and Eustachian tube insertion, 2 patients required tracheostomy, 4 had hernia repair, 2 had ventriculo-peritoneal shunt, and 1 patient required a prosthetic mitral valve replacement.

Five patients received weekly ERT (Naglazyme), 1 mg/kg/dose. Three of those patients were siblings from family 2. The first treated sibling was started on the treatment at the age of 12 outside our medical facility and died at home of a sudden cardiorespiratory arrest. Her clinical data during the treatment period was not available for us. The second sibling was started at 13 years of age and died 5 months later as result of her underlying disease. She displayed no response to the treatment. The third affected sibling was commenced on ERT at 7 years of age and died after 6 years of treatment from a progressive respiratory failure. The affected child from family 6 was treated at 15 years of age and died after 2 years as a result of her disease complications. The patient from family 5 was started at 3 years of age and continued to receive ERT (Table 2 for more detail).

One patient had bone marrow transplantation (family 4) from a full-matched heterozygous sibling (Table 3 for more detail).

Table 1 The demographic data of the patients

Family	Family Size	Number affected	Male	Female	Alive	Dead	Geographic location	Genotype
1	13	4	2	2	0	4	Al-Hofuf	p.Y251Xc.753C>G
2	7	5	2	3	0	5	Al-Hofuf	p.Y251Xc.753C>G
3	21 (large kindred)	6	4	2	0	6	Al-Hofuf	p.Y251Xc.753C>G
4	7	1	1	0	1	0	Al-Hofuf	p.Y251Xc.753C>G
5	2	1	0	1	1	0	Al-Hofuf	p.Y251Xc.753C>G
6	2	1	0	1	0	1	Abha	c270_274del5bp pc.91Afs*34
Total	52	18	9	9	2	16		
Age in years (mean)					9.5–15.5 (12.5)	0.25–20 (11.6)		

Discussion

Mucopolysaccharidosis VI (MPS VI) has been described as a rare disorder. However, the reported birth prevalence studies were based on clinical identifications and regional birth rate which may significantly underestimate the real prevalence. They range from 1 in 43,261 births in Turkish immigrant to Germany (Baehner et al. 2005) to 1 in 1,505,160 births in Sweden (Malm et al. 2008).

The prevalence of lysosomal storage diseases (LSDs) in general and MPS VI in particular in Saudi Arabia had not been studied. However, given the high consanguinity rate in this population, one should anticipate an increased frequency for those disorders in comparison to other populations (el-Hazmi et al. 1995). A retrospective analysis of all patients diagnosed with inborn errors of metabolism from 1983 to 2008 at our medical center revealed that 30% had LSDs (74/248) (Moammar et al. 2010). Mucopolysaccharidoses were the most common diagnosed disorders (28/74), and 46% represented by MPS VI (13/28). The calculated prevalence for MPS VI during the studied 28 years was 1 in 12,753 (13/165,530 live births). Twelve out of thirteen of these patients came from a geographically isolated area in the Eastern Province of the Saudi Arabia with one identified allele (p.Y251X) in the ARSB gene. This mutation was described previously in a Saudi patient with a severe phenotype (Sillence et al. 2011).

MPS VI is characterized by clinical heterogeneity with a wide spectrum of clinical manifestations which ranges from a mild to a severe phenotype (Valayannopoulos et al. 2010). The large number of identified mutations where most of them are either novel or private makes the phenotype-genotype correlation difficult. However, certain alleles described in the literature were associated with severe phenotype (Karageorgos et al. 2007; Saito et al. 2012). However, a common missense founder mutation (p.H178L) with a high frequency rate was identified in a rural isolated community in Northeast Brazil (Costa-Motta et al. 2014). Our studied population follows the same path where a consanguineous planned marriage is a

common tradition in such a geographically isolated community. All of our described patients homozygous for both p.Y251X and c270_274del5bp pc.91Afs*34 genotypes had followed the rapidly progressive severe phenotype with a mean mortality within the second decade of life.

High urinary GAG values were found to be correlated with clinical parameters indicating more rapidly progressive disease such as short stature, lower body weight, and impaired endurance as measured by a 6-min walk (Swiedler et al. 2005). Therefore, this biochemical parameter was advocated as an important indicator for the severity and the evaluation of patients with MPS VI. Urinary GAG values were available only for 5 of our patients and ranged from 586.2 to 941.6 µg GAG/mg creatinine predicting the rapidly progressive phenotype.

Cardiac involvement in the form of valvular disease was present in all of our patients studied with echocardiogram supporting the former reported data. Interestingly, cardiac disease was the presenting clinical manifestation in two of them. Cardiac involvement was found to be the predominant phenotype in MPS VI patients homozygous for p.R152W mutation in the ARSB gene (Jurecka et al. 2013).

MPS VI shares many signs and symptoms with other types of mucopolysaccharidoses, mucopolipidosis II, and multiple sulfatase deficiency. With the availability of an enzyme replacement therapy, there is much greater need for accurate and early diagnosis. The composition of GAGs in the urine may be helpful in differentiating between them. MPS I typically has increased concentration of both dermatan sulfate (DS) and heparan sulfate compared to 100% excretion of DS in MPS VI. However, demonstrating decreased enzyme activity in either cultured fibroblasts or isolated leukocytes is considered the gold standard test for the diagnosis. Seven of our patients (39%) were initially misdiagnosed with Hurler syndrome.

Until recently, supportive care and hematopoietic stem cell transplantation (HSCT) were the only available treatment modalities for MPS VI (Giugliani et al. 2007). Supportive care is mainly focused to treat the symptoms and the systemic complications. This includes occupational therapy, nutritional,

Table 2 Clinical data of patients received ERT

	Family 2		Family 5		Family 6	
Age of diagnosis (year)	3		3		2	
Genotype	p.Y251X		p.Y251X		c270_274del5bp pc.91Afs*34	
Time of ERT (year)	0	6	0	6	0	2
Age (year)	7	13	3	9	15	17
Height cm (%)	90	87	85	97	100	100
ENT complication	Recurrent URI, OM	Unchanged	Recurrent URI	Improved	Recurrent URI, OM	Less frequent
Respiratory	Recurrent admission with chest infection, sleep apnea, orthopnea	Progressive, BiPAP during night sleep	An episode of chest infection required mechanical ventilation	Asymptomatic	Mild orthopnea, on BiPAP during night sleep	Progressive
Cardiovascular system	Multiple valve disease	Progressive aortic valve stenosis, RV diastolic dysfunction	Multiple valve disease, recurrent cyanotic spells, FS—20%	No cyanotic spells Echo—stable	Mild TVI, MVI, PVI, Normal LV function	Stable
Skeletal Deformities	Severe	Unchanged	Moderate	Stable	Severe deformities	Unchanged
Ophthalmological	Corneal opacity/blind	Unchanged	Corneal opacity with congenital glaucoma	Stable	Corneal opacity, severe visual impairment	Stable
CNS	Compressive myelopathy, lower-limb weakness	Unchanged	Obstructive hydrocephalus, V-P shunt, C3–C4 compressive myelopathy	Stable	Compressive myelopathy, lower-limb weakness	Unchanged
Physical Activity	Wheelchair dependent	Unchanged	Limited	Normal for age	Wheelchair dependent	Deteriorating due to progressive skeletal pain
Urine GAG (6 µg GAG/mg creatinine)	805	295	946	308	Not available	241
Outcome	Died at 13 years of age		Continued to receive ERT		Died at 17 years of age	

URI upper respiratory infection, *OM* otitis media, *MVI* mitral valve insufficiency, *TVI* tricuspid valve insufficiency, *PVI* pulmonary valve insufficiency, *BiPAP* bilevel positive airway pressure, *V-P* ventricular–peritoneal

Table 3 Clinical outcome of patient subjected to BMT (family 4)

Age	5 1/2 years	15 1/2 years
Ophthalmological	Mild corneal opacity	Stable
ENT complication	Recurrent otitis media	None
Respiratory	Recurrent chest infection	None
Cardiovascular system	Mitral valve insufficiency /prosthetic valve replacement	Stable
Skeletal	Dysostosis multiplex	Genu valgum correction
Height cm (%)	94	125
Others	Umbilical hernia repair	Umbilical hernia repair
Urine GAG (6 µg GAG/mg creatinine)	769	211

and variable surgical procedures (orthopedic surgical repair, hernia repair, tonsillectomy/adenoidectomy, tracheostomy, cardiac valves replacement, ventriculoperitoneal shunt, spinal cord decompression, and others). The majority of our described patients had required at least one of those surgical interventions. Seven of the 18 patients (39%) had tonsillectomy/adenoidectomy and Eustachian tube insertion.

HSCT has been used rarely worldwide for MPS VI patients. A long-term follow-up study had documented a resolution of visceral complications such facial coarseness, cardiac involvement, and decreased urinary GAGs excretion. However, the skeletal deformities had persisted or even progressed in those patients (Herskhovitz et al. 1999). One of our patients had received a bone marrow transplant from a full-matched heterozygous sibling at 5 1/2 year of age. Eight years follow-up for this patient confirmed those former reported clinical and biochemical outcome.

Enzyme replacement therapy (ERT) using recombinant human rhASB for MPS VI was produced and has been marketed as the drug Naglazyme (galsulfase). A twenty-four-week phase 3 double-blind multinational clinical trial demonstrated significant improvements in endurance on a 12-min walk test and 3-min stair climb and significant reduction in urinary GAGs level (Harmatz et al. 2006). A long-term follow-up to 5 years showed that the improvement in endurance and reduction in urinary GAGs level, positive effect on puberty, growth, and pulmonary function were maintained (Harmatz et al. 2008). A sibling pair-follow-up study showed lack of skeletal deformities and cardiac valve involvement in neonate diagnosed at birth and treated early (McGill et al. 2009). Unfortunately, all of our patients had their treatment started relatively late. A long-term follow-up of the 3 survived patients from 2 to 6 years demonstrated deterioration of the respiratory symptoms in 2, and improvement in 1 (treated earlier at 3 years). Cardiac involvement was stable in two

and progressed in one patient (treated at 7 years). Physical function improved significantly only in the patient treated early. Other clinical parameters including skeletal deformities, and corneal opacity as was anticipated, did not change with the treatment. Pre-pubertal growth velocity was arrested in the patient treated late and sub-optimal in the one treated earlier. Pre- and post-treatment urinary GAG levels were available in 2 patients and showed significant improvement.

This report demonstrated the homogeneity of the phenotype and genotype of our studied population with MPS VI. Selective asymptomatic carrier testing and future newborn screening should be feasible utilizing the identified genotype. With the advent of ERT, early recognition and accurate diagnosis of this rare lysosomal storage disease are mandatory for a better and successful outcome. Newborn screening for MPS VI should be advocated in this selective high-risk population.

Compliance with ethical standards The study was approved by the Johns Hopkins Aramco Healthcare (JHAH) institution Review Board (IRB).

Conflict of interest The authors declare that they have no competing interests.

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