The Clinical and Genetic Spectrum of Maroteaux-Lamy Syndrome (Mucopolysaccharidosis VI) in the Eastern Province of Saudi Arabia

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Introduction

Mucopolysaccharidosis (MPS VI), or Maroteaux-Lamy syndrome (MIM#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 glacosaminoglycans dermatan sulfate and chondroitin sulfate. Deficiency or lack of this enzyme activity leads to a progressive intracellular accumulation of the glucosaminoglycans resulting into an irreversible multiorgan dysfunction and premature mortality.

MPS VI is characterized by a wide spectrum of clinical manifestations as with all MPSs, that includes skeletal deformities (dysostosis multiplex) with stunted growth, coarse facial features, corneal opacity, hepatosplenomegaly, cardiac abnormalities, and usually a normal cognitive function (Valayannopoulos, et al., 2010). The severe phenotype may have onset at birth with progressive severe skeletal deformities and mortality within the second decade of life. A slowly progressive phenotype has a later onset in life with mild skeletal deformities and a survival up to the fifth decade of life. Since identification of the gene (ARBS), more than 150 mutations have been described. Most of these mutations are either novel, 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 treatments available for MSVI 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 documented the restoration of normal enzyme activity with good visceral improvement. However, skeletal abnormalities remained a major problem for these patients (Herskhovitz, et al., 1999).

Naglazyme (Galsulfase) was approved as an Enzyme Replacement Therapy (ERT) for MPSVI in May 2005 and was considered a safe and effective treatment (Harmatz P., et al., 2006). Case series show 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 early detection and diagnosis with immediate intervention are crucial for a better outcome.

This study reports on 18 Saudi Arab patients from six unrelated, consanguineous families seen and diagnosed at Johns Hopkins Aramco Healthcare from January 1, 1983 to December 31, 2013. Five of these families are inhabitants of the Al-Hasa area, the largest oasis in Saudi Arabia located in the Eastern Province. One family originated from Abha (in the south of Saudi Arabia). Five patients received ERT, and one received a bone marrow transplantation from a full matched heterozygous sibling. The clinical course and outcomes for this homogenous group of patients are described.

Methods

The files of all the patients seen and diagnosed with MPS VI (Maroteaux-lamy Syndrome) at the main hospital from January 1st, 1983 to December 31st, 2013 were reviewed. The study was approved by the institutional review board.

The patients were suspected to have MPS because of 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, USA, or Wilink 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.

Results

A total of 18 patients from 6 unrelated, consanguineous families were diagnosed with MPS VI during the defined 30 year period with an average of three affected children per family. Five of those families were inhabitants of Al-Hasa. All of the tested, affected individuals from these families were found to be homozygous for c.753C>Gp.Y251X mutation in the ARBS gene. The four affected children and the father of Family one died before the genetic study had become available. However, the mother was confirmed to be heterozygous for this common mutation. Family six originated in Abha (in the south) with one affected child who was to be homozygous for c270_274del5bp pc.91Afs*34 mutation (Table 1).

Five patients received weekly enzyme replacement therapy (Naglazyme), 1 mg/kg/dose. Two siblings were started on the treatment at the age of 12 and 13 years respectively. Both died after 5 months of commencing the treatment secondary to complications of their underlying disease. Three patients continued to receive the therapy and long-term, follow up data is available on them (Table 2).

One patient had a bone marrow transplantation from a full matched heterozygous sibling (Table 3).

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)		

Table 1: Demographic Patient Data

	Family-2		Family-5		Family-6	
Age of Diagnosis	3 year		3 year		2 year	
Genotype	p.Y251X		p.Y251X		c270_274del5bp pc.91Afs*34	
Time of ERT (year)	0	6	0	6	0	2
Age (year)	7 years	13 year	3 years	9 years	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 orhtopenea, on BiPAP during night sleep	Progressive
Cardiovascular System	Multiple Valves disease	Progressive Aortic Valve stenosis, RV diastolic dysfunction	Multiple Valves 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 limbs weakness	Unchanged	Obstructive hydrocephalus, V-P Shunt, C3-C4 compressive myelopathy	Stable	Compressive myelopathy, lower limbs weakness,	Unchanged
Physical Activity	Wheelchair dependent	Unchanged	Limited	Normal for age	Wheelchair dependant	Deteriorating due to progressive skeletal pain
Urine GAG (6µg 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	

Table 2: Clinical Data of Patients who Received ERT

Age	5 ½ years	15 ½ 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 (6µg GAG/mg Creatinine)	769	211

Table 3: Clinical Outcome of Patients Subjected to BMT (Family 4)

Conclusions

This report demonstrates the homogeneity of the phenotype and genotype of our population with MPS VI. Selective asymptomatic carrier screening should be offered utilizing this identified genotype. With the advent of ERT, early recognition and accurate diagnosis of this rare lysosomal storage disease is mandatory for better and successful outcomes. Newborn screening for MPS VI should be advocated in this selective, high-risk population.

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