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Clinical features of Mexican patients with Mucopolysaccharidosis type I

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ABSTRACT. Mucopolysaccharidosis type I (MPS-I) is an autosomal recessive lysosomal storage disorder caused by a deficiency or absence of α-L-iduronidase, which is involved in the catabolism of glycosaminoglycans (GAGs). This deficiency leads to the accumulation of GAGs in several organs. Given the wide spectrum of the disease, MPS-I has historically been classified into 3 clinical subtypes - severe (Hurler syndrome), intermediate (Hurler-Scheie syndrome), and mild (Scheie syndrome) - none of which is determined by residual enzyme activity. Eleven Mexican patients with MPS-I from northwestern México were evaluated. Diagnoses were confirmed through quantification of GAGs in urine and enzyme assay for α-L-iduronidase. Regardless of phenotype, all patients had various degrees of infiltrated facies, short

stature, dysostosis multiplex, joint contractures, and corneal opacity typical of the disease. A better understanding of the spectrum of this disease can assist in diagnosis, treatment, and improvement in the quality of life for these patients.

Key words: Mucopolysaccharidosis I; Glycosaminoglycans; α-L-Iduronidase; Hurler syndrome; Scheie syndrome; Mexican population

INTRODUCTION

Mucopolysaccharidosis type I (MPS-I) is an autosomal recessive disease caused by a deficiency of the lysosomal enzyme α-L-iduronidase (IDUA; E.C. 3.2.1.76). This deficiency leads to the accumulation of undegraded glycosaminoglycans, mainly dermatan and heparan sulfates, in tissues and their excess excretion in urine (Neufeld and Muenzer, 2001). MPS is a rare, pan-ethnic disease with an incidence of 1/100,000 live births (Meikle et al., 1999). No epidemiological studies of this disease have been carried out in Mexico, and its behavior and predominant mutations in this population remain unknown. MPS-I has been clinically classified into 3 subtypes. Distinguishing one phenotype from another usually requires assessment of 3 aspects: age of onset of symptoms, neurological impairment, and involvement of organs and systems. The severe phenotype is the Hurler syndrome, with early onset and survival of <10 years; the Scheie phenotype is the mildest, and it involves mild skeletal deformities, stiff joints, no mental retardation, and normal life expectancy. Hurler-Scheie, an intermediate phenotype, is characterized by moderate mental impairment and life expectancy of <25 years. Recently, the term severe MPS-I has been suggested to describe patients with early onset and rapid progression, whereas attenuated MPS-I is the suggested term for the milder phenotype and longer life span during the disease course (Wraith, 1995; Neufeld and Muenzer, 2001). Phenotypic heterogeneity is thought to be caused by various combinations of mutations of the IDUA gene (OMIM 252800), but other possible explanations are nonpathogenic polymorphism, residual enzymatic activity, the presence of alternative substrates, modifying genes, and environmental factors that can contribute to difficulty in understanding genotype-phenotype correlation (Scott et al., 1993; Venturi et al., 2002; Pereira et al., 2008).

A typical clinical presentation includes coarse facial features, short stature, hepatosplenomegaly, dysostosis multiplex, corneal clouding, stiff joints, hearing loss, restrictive lung disease, upper airway obstruction, valvular heart disease, communicating hydrocephalus, spinal cord compression, and mental retardation of varying degrees (Wraith, 1995; Nyhan et al., 2005; Vijay and Wraith, 2005). All subtypes of MPS-I have a wide range of enzyme activity levels, from just below the normal lower limit to undetectable. The IDUA gene has been mapped at 4p16.3. It is approximately 19 kb and contains 14 exons, and its messenger RNA transcript is 2.3 kb and encodes a precursor protein of 653 amino acids (Scott et al., 1990). To date, more than 110 mutations (nonsense, missense, splice site, deletions, and insertions) have been identified throughout the gene. Two mutations, W402X and Q70X, are present in more than 60% of white patients (Bunge et al., 1994; Scott et al., 1990, 1995; Li et al., 2002; Matte et al., 2003; Guven et al., 2008). The available treatment for MPS-I patients is currently hematopoietic stem-cell transplantation before the age of 2 years. Enzyme replacement therapy with recombinant human IDUA reduces and prevents the accumulation of undegraded substrate. It is indicated for the long-term treatment of non-neurological

manifestations because it ineffectively crosses the blood-brain barrier and has few effects on the central nervous system (Wraith 2005; Wraith et al., 2005; Beck, 2010). The purpose of this study was to describe the epidemiological aspects and most common clinical manifestations of a group of Mexican patients with MPS-I.

MATERIAL AND METHODS

Our sample included 11 patients with MPS-I (median age 8.6 years; 3 males and 8 females). Six had the severe phenotype (Hurler syndrome) and 5 had the attenuated phenotype (4 Hurler-Scheie and 1 Scheie). Clinical classifications were based on the age of onset, neurological damage, and involvement of organs and systems. The patients were studied over 2 years (February 2008 to June 2010). MPS-I was suspected based on clinical and radiological features and confirmed with excessive urinary excretion of glycosaminoglycan (Gallegos-Arreola et al., 2000) and enzyme assay deficiency for IDUA using the dried blood spot test. A medical history, complete physical examination, laboratory testing, and X-ray studies were obtained for all patients, and each was assessed using the clinical criteria of the latest Mexican MPS consensus (Grupo de Consenso de la Mucopolisacaridosis Tipo I, 2008).

RESULTS

The average age of symptom onset was 12 months (range, 2-36 months); for patients with the severe phenotype, the average was 7 months (range, 2-12 months), and for those with the attenuated phenotype, the average was 1.6 years (range, 3-36 months). The earliest diagnosis was made at 4 months in a patient with the severe phenotype and a history of an affected sibling. Diagnosis within the 1st year of life occurred in 27% (3/11); for patients with the severe phenotype, the average age of diagnosis was 2.1 years (range, 4-58 months), whereas that for patients with the attenuated phenotype (5/11) was 7.6 years (range, 12-192 months). The demographic and clinical features of the patients are shown in Tables 1 and 2.

Table 1. Characteristics of the patients with MPS-I.

Case	Gender	Age	Consanguinity	Age of onset of symptoms	Age at diagnosis	GAGs (22) (0.135 ± 0.35 mg/dL)	α-L-iduronidase (2.2-11.7 µM)	Phenotype
1	F	4.1 y	-	3 m	18 m	0.279	0.4	H
2	F	5.6 y	-	2 m	13 m	0.247	0.4	H
3	F	5.1 y	-	16 m	24 m	0.151	0.3	H-S
4*	F	8 m	+	6 m	4 m	0.167	0.3	H
5*	F	13 y	+	11 m	12 m	0.208	0.3	H
6	F	15 y	-	6 m	54 m	0.455	0.4	H
7	F	16 y	-	36 m	16 y	0.150	1.5	S
8	M	7.7 y	-	12 m	5 y	0.230	0	H-S
9	M	1.8 y	-	3 m	1 y	0.105	0.86	H-S
10	M	5 y	+	12 m	4 y 10m	0.956	0	H
11	F	14 y	-	24 m	14 y	0.187	0.9	H-S

(*) sisters, +: present, m: months, y: years, GAGs: glycosaminoglycans, H: Hurler, H-S Hurler-Scheie, S: Scheie.

Clinical presentation

Facial dimorphism was a constant feature in patients with the severe MPS-I phenotype: infiltrated coarse features were present in 100% of patients with various degrees of severity. Short stature was present in 91%, and 27% had macrocephaly.

Table 2. Clinical features of MPS patients.

Clinical features	Severe phenotype N = 6 (%)	Attenuated phenotype N = 5 (%)	Total (N = 11) (%)
Physical appearance			
Coarse facial features	6 (100)	5 (100)	11 (100)
Wide and short thorax	6 (100)	5 (100)	11 (100)
Short stature	6 (100)	4 (80)	10 (91)
Macrocephaly	2 (33)	1 (20)	3 (27)
Skeletal abnormalities			
Dysostosis multiplex	6 (100)	5 (100)	11 (100)
Short neck	6 (100)	5 (100)	11 (100)
Joint stiffness	6 (100)	5 (100)	11 (100)
Claw hand	6 (100)	4 (80)	10 (91)
Genu valgum	6 (100)	3 (60)	9 (82)
Dorsolumbar kyphosis	5 (83)	1 (20)	6 (55)
Femoral dysplasia	3 (50)	3 (60)	6 (55)
Scoliosis	3 (50)	1 (20)	4 (36)
Ophthalmologic features			
Corneal clouding	6 (100)	5 (100)	11 (100)
Visual disability	3 (50)	1 (20)	4 (36)
Glaucoma	3 (27)	0	3 (27)
Megalocornea	1 (17)	0	1 (9)
Respiratory and otolaryngologic feacture			
Snoring	6 (100)	4 (100)	10 (91)
Chronic rhinitis and/or sinusitis	5 (83)	3 (60)	8 (73)
Adenotonsillar hypertrophy	5 (83)	2 (40)	7 (64)
Sleep apnea	5 (83)	2 (40)	7 (64)
Chronic otitis media	4 (67)	2 (40)	6 (55)
Sensorial, conductive or mixed hearing loss	3 (50)	3 (60)	6 (55)
Wheeze	4 (67)	1 (20)	5 (45)
Sinobronquial syndrome	1 (17)	0	1 (9)
Bronchial hyperreactivity	1 (17)	0	1 (9)
Gastrointestinal features and abdominal wall			
Hepatomegaly	6 (100)	3 (60)	9 (82)
Splenomegaly	5 (83)	1 (20)	6 (55)
Umbilical and inguinal hernia	5 (83)	3 (60)	8 (73)
Chronic diarrhea	2 (33)	2 (40)	4 (36)
Recurrent hernia	4 (67)	0	4 (36)
Diastasis recti	2 (33)	0	2 (18)
Cardiac features			
Healthy heart	4 (67)	4 (80)	8 (73)
Valvular disease	2 (33)	1 (20)	3 (27)
Neurological features			
Mental retardation	6 (100)	1(20)	7 (64)
Hydrocephaly	4 (67)	0	4 (36)
Attention deficit disorder	2 (33)	0	2 (18)
Progressive compression of the spinal cord	1 (17)	0	1 (9)
Increased intracranial pression	1 (17)	0	1 (9)
Epilepsy	1 (17)	0	1 (9)
Dermathologic features			
Thick hair	6 (100)	3 (60)	9 (82)
Thick skin	6 (100)	2 (40)	8 (73)
Hypertrichosis	5 (83)	1 (20)	6 (55)
Persistent Mongolian spots	3 (50)	1 (20)	4 (36)

Skeletal features

The musculoskeletal manifestations were the most constant regardless of the phenotype. Dysostosis multiplex, short neck, and joint contractures were present in 100% of cases. Besides, the characteristic claw hand and *genu valgum* was observed in 100% of patients with the severe phenotype. Thoracolumbar kyphosis, recognized as an early feature, was present in 83% of patients with the severe phenotype. Femoral dysplasia and scoliosis were present in 50 and 60%, respectively, in patients with the severe phenotype, and in 60 and 20%, respectively, of those with the attenuated phenotype.

Ophthalmic features

All patients had corneal opacity independent of the phenotype. Thirty-six percent had decreased visual acuity, and 3 cases of glaucoma and 1 case of megalocornea (severe phenotype) were recorded.

Cardiovascular features

Within the patient group, 73% were asymptomatic for cardiovascular manifestations. The valvular disease was present in 2 patients with the severe phenotype (33%) and 1 patient with the attenuated phenotype (20%).

Respiratory and otolaryngologic features

Respiratory and otolaryngologic manifestations were more common in patients with the severe phenotype; however, all patients displayed snoring at some time during the disease. Chronic rhinitis or sinusitis, adenotonsillar hypertrophy, and sleep apnea were observed in 83% of patients with the severe phenotype, chronic rhinitis or sinusitis was present in 60%, and 40% with the attenuated phenotype had adenotonsillar hypertrophy and sleep apnea. Some degree of hearing loss was present in 55% (6/11), but none of the subjects was deaf.

Gastrointestinal and abdominal wall features

Hepatomegaly was present in 82% and splenomegaly in 55% of patients. Umbilical and inguinal hernias accompanied both phenotypes (73%), whereas chronic diarrhea was observed in 36%.

Neurological features

All of the patients with the severe phenotype had mental retardation, but only 20% (1/5) of patients with attenuated phenotypes showed mild to moderate mental retardation. The following neurological manifestations were observed only in patients with the severe phenotype: hydrocephalus (67%), hyperactivity (33%), and progressive spinal cord compression, intracranial hypertension, and epilepsy (17%). Although carpal tunnel syndrome has frequently been reported among MPS-I patients, it was absent in our study group.

Dermatological features

Thick hair and skin were the most common features observed in both phenotypes: 83% (severe) and 73% (attenuated). Hypertrichosis was present in 87% of patients with the severe phenotype and 20% of those with the attenuated phenotype. The persistence of Mongolian spots was present in 50% of patients with the severe phenotype and 20% of patients with the attenuated phenotype.

DISCUSSION

MPS-I has traditionally been classified into 3 phenotypes: Hurler, Hurler-Scheie,

and Scheie, but no clinical or biochemical criteria define the conventional boundaries of these classifications. The severe phenotype (Hurler) represents the most serious of all clinical manifestations, including neurologic impairment. Currently, the tendency is to recognize only 2 phenotypes, severe and attenuated, although factors that might predict the clinical course of the disease, including biomarkers, remain elusive. No comprehensive epidemiological studies that establish the incidence of this disease have been conducted in México. The severe phenotype was most frequently observed in this study, as has been reported in other publications (Alif et al., 2000; Cimaz et al., 2006). This predominance can be explained by the apparent clinical features of the severe phenotype; patients with the attenuated phenotype who lack mental retardations are often underdiagnosed. Although MPS-I is an autosomal recessive disease, our study showed that the female gender was predominant in a ratio of 5:1, and in general, the onset of symptoms occurred on average by the age of 1 year. However, the onset of symptoms in the severe phenotype was 8 months, as reported by others (Vijay and Wraith, 2005).

For patients with the attenuated phenotype, the average age of symptom onset was 1.8 years, although the age of onset up to 2.9 years has been reported, with an earlier diagnosis made in 27% of cases (Vijay and Wraith, 2005). In the same series of patients, Vijay and Wraith (2005) have reported an average age of symptom onset of 7.6 years in the severe phenotype, with an average age of diagnosis of 9.17 years (range 15 months - 40 years). Notably, late diagnosis in that series was related to delays in some patients whose parents did not seek medical attention and ignorance of the disease by the physician. These possibilities are important to take into account because the earlier the diagnosis is made, the sooner the treatment can begin to improve the quality of life.

The clinical manifestations in patients in the present study were similar to those reported in other studies, but the frequencies differed. Physical appearance, a significant aspect of diagnosis, was present in 100% of patients and included infiltrating facies, short stature, dysostosis multiplex, joint contractures, and corneal opacity. Mental retardation was present in 100% of patients with the severe phenotype but only 20% of those with the attenuated phenotype. This feature is among the most important signs to be evaluated. Mental retardation in patients with the attenuated phenotype was mild to moderate. The remaining neurological manifestations were present only in the severe phenotype.

Skeletal abnormalities were among the most constant features, but joint contractures in patients with the attenuated phenotype may be the earliest and most important clinical manifestation (Alif et al., 2000). Corneal opacity, present in 100% of the patients in this study, may not be a constant feature. Alif et al. (2000) have reported it in 80% of cases, taking into account that loss of brightness in the eyes may be the first sign of disease. However, other eye abnormalities such as thickening of the sclera and optic nerve sheath, which occur earlier, must be investigated even before additional clinical features appear (Schumacher et al., 2008). Respiratory and otorhinolaryngologic manifestations were more frequent in patients with the severe phenotype because, in addition to airway obstruction, other factors such as macroglossia were involved and craniofacial abnormalities contributed to repetitive pathologies of the upper airway. Visceromegaly was a common clinical sign among MPS-I patients: 82% had hepatomegaly and 55% had splenomegaly in addition to umbilical or inguinal hernias, some of which were recurrent in the severe phenotype (67%). Accumulated substrate on the skin and annexes leads to the skin and hair thickening (100%) and hypertrichosis (83%) observed in the severe phenotype. Persistent Mongolian spots, which have frequently been reported in other series, were present in only 36% of patients in our study.

Early diagnosis in patients with MPS-I is essential for forecasting quality of life. Therefore, knowing the clinical spectrum of patients with what is referred to as a rare disease is important. Health personnel should be trained for accurate diagnosis. Now that hematopoietic cell transplantation and enzyme replacement therapy have been introduced, the coming years should bring changes in the natural history of the disease. Current therapeutic challenges such as reducing substrate and the use of intrathecal replacement therapy as an effective alternative therapy for central nervous system manifestations are expected to increase the quality of life and life expectancy in these patients. Genetic counseling and identification of carriers are essential in families with a history of the disease.

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