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Profile of Egyptian Patients with Mucopolysaccharidosis

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ABSTRACT

Background: Mucopolysaccharidoses (MPS) are chronic progressive lysosomal disorders (Six distinct types) which are inherited as autosomal recessive except MPS II which is inherited as X-linked recessive disorder

Patients and Methods: This study is designed to investigate a group of Egyptian patients with MPS biochemically using screening test by electrophoretic separation of glycosaminoglycans and enzymatic assay in order to establish the diagnosis of the disorder and its subtypes, to prepare patients for enzyme replacement therapy. Also this will help in proper genetic counseling and prenatal diagnosis. Establishing a reliable rapid screening test for MPS is another aim of the study. The present study included 20 index cases suspected clinically as mucopolysaccardioses at the Medical Genetics Center, Ain Shams University (ASUMGC).They were subjected to full history taking, thorough clinical examination, family pedigree construction, skeletal survey, abdominal ultrasound and echocardiography, quatitative assay of glycosaminoglycans (GAGs) by diemethylmethlene blue (DMB) is done.

Results: The level of urinary GAGs by two dimentional electrophoresis (DMB) test was high in all patients tested. After that the patients were subjected to 2-DEP to determine the pattern of GAGs for probable type of MPS. 11 cases (55%) showed big dermatan sulfate spot (Type I, II or VI). Seven cases (35%) showed hepran sulfate spot (Type III), 2 cases (10%) showed keratan sulfate spot (Type IV). Finally patients were subjected to enzyme analysis specific for each type of MPS to confirm diagnosis. Reaching a specific diagnosis is of importance for genetic counseling and prenatal diognosis which is possible for all types of MPS.

Conclusion: Prenatal diagnosis was done by 2-DEP of the amniotic fluid for four mothers of affected patients of MPS. One fetus was proved to be affected with MPS III. Another fetus was affected with MPSII. The others fetuses were normal.

Key Words:

Mucopolysaccharidosis, Egypt.

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INTRODUCTION

The mucopolysaccharidoses (MPS) are a group of heritable disorders each of which is produced by a deficiency of an enzyme required for the lysosomal degradation of sulfated glycosaminoglycans.[1]

Mucopolysaccharides (or glycosaminoglycans) are large macromolecules composed of repeating frequently sulfated, disaccharide units attached to a protein core. A series of lysosomal acid hydrolases degrades the glycosaminoglycans by step-wise removal of the sulfates and carbohydrate residues.[1]

There are 10 known enzyme deficiency that give rise to six distinct MPS. Most of these enzymes have been extensively purified, their biosynthesis and processing have been elucidated and their primary structure determined from the sequence of the corresponding cDNA. MPS I (Hurler, Hurler-Scheie, Scheie) is due to deficiency of lysosmal hydrolase, α-l-iduronidase. In MPS II (Hunter syndrome) the deficient enzyme is iduronate sulphatase. As regards MPS III (Sanfilippo syndrome, subtypes A, B, C and D) is due to deficiency of 4 enzymes, heparan–N–sulfatase, α–N–acetyl glucosaminidase, acetyl transferase, α–N–acetyl glucosamine–6–sulfatase). MPS IV (Morquio syndrome, A & B subtypes) is due to deficiency of 2 enzymes, N–acetylgalactosamine–6–sulfatase and B–galactosidase. MPS VI (Marteaux-Lamy Syndrome) is due to deficiency of N-acetylgalactosamine-4-sulfatase (Aryl sulphatase). MPS VII (Sly syndrome) is due to deficiency of β–glucuronidase. MPS IX is due to deficiency of hyluronidase.[2]

Clinical symptoms eventually result from the lysosomal storage of the partially degraded glycosaminoglycans.[3]

Incompletely degraded glycosaminoglycans accumulate in multiple organ systems leading to progressive worsening of the clinical manifestation. MPS share many clinical features, though in variable degrees. These include a chronic and progressive course, multisystem involvement, organomegaly, dystosis multiplex and abnormal facies. There is clinical similarity between different enzyme deficiencies and conversely a wide spectrum of clinical severity within any one enzyme deficiency.[2]

Disorders that result in heparan sulfate storage have progressive central nervous system involvement. Affected patients may have macrocephaly and develop communicating hydrocephalus. Dermatan sulfate storage is associated with progressive visceral and bone involvement. Affected patients may have hepatosplenomegaly, cardiomyopathy or cardiac valvular involvement.[2]

The first line to diagnose MPS is the quantitative assay of excessive urinary GAGs by diemethylmethlene blue (DMB) test and qualitative assay of urinary GAGs by two-dimensional electrophoresis (2-DEP) to determine the probale MPS type. Definite diagnosis is established by enzyme assay. Because lysosomal enzymes are present in all

cells except mature erythrocytes, the deficiency can be determined in a variety of cells and body fluids. Cultured fibroblasts, leukocytes or serum are generally used. The choice depends on the particular enzyme.[1]

Also the 2-DEP is applicable for prenatal diagnosis after amniocentesis and enzymatic assay in the fetus is done for chrionic villus biopsy specimen.[1]

AIM OF THE WORK

This study was designed to investigate the profile of a group of Egyptian patients with mucopolysaccharidoses (MPS) and its subtypes, to prepare patients for enzyme replacement therapy. This will help in proper genetic counseling and prenatal diagnosis. Establishing a reliable rapid screening test for MPS is another aim of the study.

PATIENTS AND METHODS

Twenty cases suspected clinically to be one of the mucopolysaccharidoses syndrome were enrolled in the current study. They were chosen from cases attending the Medical Genetics Center Out-Patient Clinic, Ain Shams University. They were subjected to the following:

- *Full history taking:* Lying stress on personal history, main complaint, developmental history, past history, family history of similar condition and parental consanguinity. History of symptoms suggestive of all body system involvement will be explored.
- *Thorough clinical examination:* including anthropometric measurements. Ocular, cardiovaslar, abdominal and neurological examinations were also done.
- *Three generations family pedigree constructions:* Illustrating paretnal consanguinity if any and similar condition among family members.
- *Skeletal survey including:* Plain x–ray of the skeleton (Skull, upper limbs, lower limbs, chest, cervical and dorsolumbar spines) to document the presence of any skeletal abnormalities suggestive of MPS.
- Ophthamological examination including slit lamp examination to detect the corneal clouding or other abnormalities of the anterior chamber & fundus examination.
- *Echocardiography:* To document any cardiac pathology (Valvular involvement and or cardiomyopathy).
- *Abdominal ultrasonogrphy:* To document any organomegaly.
- *Determination of total urinary glycosaminoglycans (GAGs):*[4] Glycosaminoglycans (GAGs) were determined quantitatively by reaction with dimethylmethylene blue (DMB) in a reaction that didn't require prior precipitation of the GAGs. The color was measured immediately at a wave length of 520nm. The DMB ratio was obtained by dividing the urine crea-

tinine with GAGs concentration in mg/l, and the ratio was expressed as mg/mmol creatinine, normal level equals 44.6±23.7 (Less than 2 years old), 15.3±13.0 (2-17 years old) and 5.2±2.5 (Adult 18-42 years of age).

- *Two dimentional electrophoresis of the GAGs (2-DEP) :*[5] Glycosaminoglycans (GAGs) were determined qualitatively by two dimentional electrophoresis to determine possible subtypes of mucopolysaccharidoses.

- The mothers of 4 studied patients with different types of MPS were subjected to prenatal diagnosis of next pregnancy using amniocentesis.

GAGs level was determined in amniotic fluid by 2- DEP.[6]

- *Enzymatic assay:* For the available enzyme of the various types of MPS to confirm the diagnosis.[7]

As a comparison group 15 apparently normal age & sex matched children were included in the study.

RESULTS

At time of examination, ages of enrolled cases ranged between 13/12-12 years with a mean age of 5.07±3.026 years. On the other hand, the age of onset of clinical manifestations ranged between 6m-2years with a mean age 1.37±1.05 years. 11 were males (55%) and 9 were females (45%).

The overall consanguinity rate recorded in the current study was 80% (16 cases). On the other hand+ve family history of a similarly affected relative was recorded in 60% (12 cases).

Table (1) Show the different clinical manifestations recorded among studied cases with different types of MPS and their frequency distribution. The most commonly detected clinical manifestations were coarse facies (85%) followed by hepatomegaly (75%), skel-

Table 1: Clinical manifestations among studied patients with different types of MPS.

MPS subtypes		*MR		Coarse facies		Corneal opacity		Heart affection		Hepatomegaly		Splenomegaly		Hernia		Skeletal manifestations	
		No	%	No	%	No	%	No	%	No	%	No	%	No	%	No	%
I	IH	2	10	2	10	2	10	2	10	2	10	2	10	2	10	2	10
	IHS	2	10	3	15	2	10	2	10	3	15	3	15	2	10	2	10
	IS	0	0	1	5	1	5	0	0	0	0	0	0	0	0	1	5
II		2	10	2	10	0	0	1	5	2	10	2	10	2	10	2	10
III		7	35	5	25	0	0	1	5	4	20	1	5	0	0	2	10
IV		0	0	1	5	1	5	0	0	1	5	0	0	0	0	2	10
VI		0	0	3	15	3	15	2	10	3	15	3	15	2	10	3	15
Total		**13**	**65**	**17**	**85**	**9**	**45**	**8**	**40**	**15**	**75**	**11**	**55**	**8**	**40**	**14**	**70**

*MR=mental retardation.

etal manifestations (70%), mental retardation (65%), splenomegaly (55%), corneal opacity (45%), heart affection (40%) and inguinal or umbilical hernia (40%).

IQ of studied patients ranged between 34-100 with a mean value 66±0.17, The mean value of IQ of different MPS types is shown in (Table 2).

Table 2: IQ distribution among studied patients with different MPS subtypes

MPS Subtypes	Range	Mean±SD
IH	34-38	36±0. 27
I IHS	60-75	68±0. 46
IS	85	
II	40-50	45±0. 24
III	35-50	40±0. 25
IV	80-100	90±0. 111
VI	90-100	95±0. 105
Total	**34-100**	**66±0.17**

Table (3) Shows the sketetal abnormalities among studied patients with different MPS subtypes and their frequency distribution. The most commonly detected skeletal abnormalilies were stiffness of the joints (60%) followed by kyphosis (50%), flaring of ribs (50%), pectus carinatum (25%), kyphoscoliosis (10%) and laxity of the joints (10%).

Table 3: Skeletal abnormalities among studied patients with different MPS subtypes.

MPS subtypes	Vertebral column				Joints				Thoracic cage			
	Kyphosis		kyphoscoliosis		Stiffness		Laxity		Pectus carinatum		Flaring of ribs	
	No	%	No	%	No	%	No	%	No	%	No	%
IH	1	5	1	5	2	10	0	0	1	5	2	10
I IHS	2	10	0	0	2	10	0	0	1	5	1	5
IS	0	0	0	0	1	5	0	0	0	0	0	0
II	1	5	0	0	2	10	0	0	0	0	2	10
III	2	10	0	0	2	10	0	0	0	0	1	5
IV	1	5	1	5	0	0	2	10	2	10	2	10
VI	3	15	0	0	3	15	0	0	1	5	2	10
Total	10	50	2	10	12	60	2	10	5	25	10	50

Results of GAGs value , 2- DEP and enzymatic assay of studied patients were shown in (Table 4), (Figure 1, 2, 3).

Table 4: Shows the detected GAGs value, results of 2-DEP, and enzymatic assay of studied patients with different MPS subtypes.

MPS Subtypes		Code No of patients	Age at time of examination	Age of onset	Sex	GAG value mg/ mmolcreatinine	2-DEP	Enzyme assay		
								Name	Normal range	Level
I	IH	1	7y	6m	Male	28	Dermatan & Hepran sulphate	α - L-Iduronidase	(10-40 µmol/gp/h)	Zero
	IH	2	3y	6ms	Female	12.2	Big Dermatan sulphate	α - L-Iduronidase	(10-40 µmol/gp/h)	1.8
	IHS	3	3 ½ y	1y	Male	15	Big Dermatan sulphate	α - L-Iduronidase	(10-40 µmol/gp/h)	1.2
	IHS	4	17/12y	1 3/12y	Female	68	Big Dermatan sulphate	α– L-Iduronidase	(10-40µmol/gp/h)	0.08
	IHS	5	11y	3y	Male	18.5	Big Dermatan sulphate	α - L-Iduronidase	(10-40 µmol/gp/h)	Zero
	IS	6	12	5y	Female	18.3	Big Dermatan sulphate	α - L-Iduronidase	(10-40 µmol/gp/h)	Zero
II		7	5y	10m	Male	34	Big Dermatan sulphate	α-L- Iduronidase Iduronate-2-sulphatase	(10-40 µmol/gp/h)(167-475nmol/4h/ml)	32 0.1
		8	7y	7m	Male	22	Big Dermatan sulphate	α –L-Iduronidase Iduronate-2-sulphatase	(10-40 µmol/gp/h)(167-475nmol/4h/ml)	10.7zero
III		9	1 6/12y	8m	Male	40	Hepran sulphate	N-acetyl -α - glucosaminidase	(10-45 µmol/L/h)	32
		10	1 9/12y	1y	Male	21	Hepran suplhate	N-acetyl -α - glucosaminidase	(10-45 µmol/L/h)	25
		11	3y	6m	Male	17.7	Hepran sulphate	N-acetyl - α - glucosaminidase	(10-45 µmol/L/h)	36
		12	4y	1 3/12y	Male	14	Hepran sulphate	N-acetyl -α - glucosaminidase	(10-45 µmol/L/h)	35.29
		13	1 8/12y	1 3/12y	Female	86.5	Hepran sulphate	N-acetyl -α - glucosaminidase	(10-45 µmol/L/h)	40.89
		14	6y	1 2/12y	Female	8.7	Hepran sulphate	N-acetyl -α - glucosaminidase	(10-45 µmol/L/h)	38.67
		15	1y	11m	Male	40	Hepran sulphate	N-acetyl -α - glucosaminidase	(10-45 µmol/L/h)	41.88
IV		16	3y	1y	Male	5.1	Kertan sulphate	Galactose -6-sulphatase	(400-2000pmol/gp/h)	71
		17	8y	1 6/12y	Female	14	Kertan sulphate	Galactose -6-sulphatase	(400-2000pmol/gp/h)	Zero
VI		18	8y	2y	Male	18	Big Dermatan sulphate	α -L- IduronidaseAryl sulphatase B	(10-40µmol/gp/h) (5-70µmol/gp/h)	24.98Zero
		19	9y	2y	Female	30	Big Dermatan sulphate	α-L- IduronidaseAryl sulphatase B	(10-40µmol/gp/h)(5-70µmol/gp/h)	34Zero
		20	4y	1 6/12y	Female	52	Big Dermatan sulphate	α-L-IduronidaseAryl sulphalase B	(10-40µmol/gp/h)(5-70µmol/gp/h)	10.9Zero

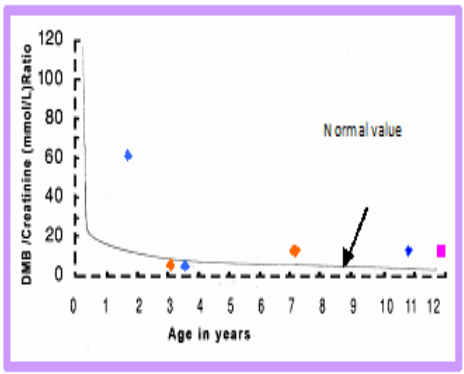

Fig. 1: GAGs value for MPS I MPS I H MPS I HS MPS I S

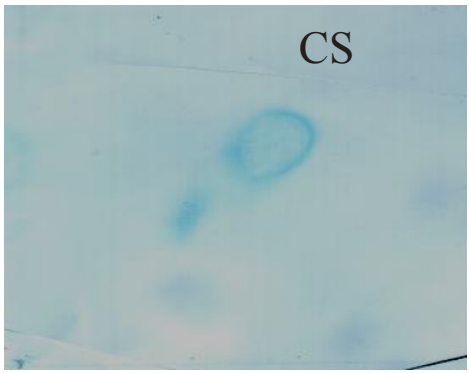

Fig. 2: Normal GAGs Pattern
CS=Chondrioitin sulphate

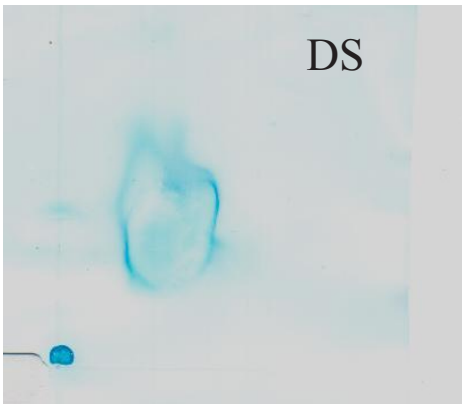

Fig. 3: Big Dermatan Sulphate Pattern
DS= dermatan Sulphate

A mother of one of studied cases with type III MPS was subjected to 2-DEP for the amniotic fluid twice (i.e. in the following two pregnancies),one of them have yielded a normal fetus. and the other was similarly affected.Another mother proved to have an affected fetus with MPS II .

DISCUSSION

The present study enrolled 20 cases of clinically,biochemically and radiologically diagnosed MPS. They were chosen from patients attending the Medical Genetic Center, Ain Shams University during the period of study. The commonest type was MPSIII (7 patients, 35%), followed by MPSI (6 patients, 30%), MPSIV (3 patients, 15%), MPSII (2 patients, 10%) and MPSVI (2 patients, 10%). No patient with MPS VII and IX were detected in this study. In another study done in Egypt by Shawky et al.[8] type VI was the commonest type (33.3%), followed by MPSIII (22.2%), MPSIV (22.2%), MPSI (11.1%), MPSII (5.5%) and MPS VII (5.5%).

There were population differences in the frequency of different types of MPS; MPS II was the most common type in Israel (1/34,000) and MPS IV in Northern Ireland (1/840,000) while Sanfilippo syndrome type B is the most prevalent type in Greece and type A in England. The aparent rarity of MPS VII may be due to frequent fetal or neonatal lethality. It is likely that the true incidence of MPS will become Known only when progress in therapy will make it desirable to institute early screening.[1]

The sex distribution among enrolled cases was 55% (11) males, 45% (9) females with male to female ratio of 1.2:1. This finding goes with the well known fact that both sexes are equally affected in autosomal recessive disor-

ders including all types of MPS except Hunter syndrome (MPS II), which is an X-linked recessive disorder.[1]

The overall consanguinity rate recorded in the current study was considerably high; 80%. Similarly Shawky et al.[8] reported a consanguinity rate of 77.1% among their studied sample of MPS.

Consanguinity is of special importance in genetic counseling of autosomal recessive disorders. Hafez et al.[9] reported a consanguinity rate of 28% and Temtamy et al.[10] reported a consanguinity rate of 36.8%, among normal Egyptians which help to accumulate deleterious genes in the families.

By definition a recessive disease, as all types of MPS except for MPS type II, requires the inheritance of a mutant allele at the same genetic locus from each parent. When the genes are rare, the likelihood of unrelated parents being carriers is rare. If the parents have a common ancestor who carried a recessive gene, the likelihood that two of the descendents inherited the same allele is enhanced, which is applicable to the current study and other similar studies in Egypt in which consanguineous marriage is a long standing tradition. The less frequent the recessive gene, the stronger the likelihood that an affected individual is the product of a consanguineous mating. On the other hand, when the recessive gene is common in the population, the probability of two unrelated parents being carriers is great enough to minimize the role of consanguinity.[2]

Martyn[11] stated that the eye is one of the most prominent organs involved in MPS. Prominent eyes, puffy eyelids, heavy eye brows and corneal clouding are the major manifestations recorded among patients with MPS. In the present study corneal cloudiness was observed in 9 cases (45%); whereas the other 11 cases had apparently clear corneas (55%). The clear cornea was found in studied cases with MPS II, III. In agreement with the pervious findings. Shawky et al.[8] reported that ocular affection of their studied patients were reported in 33.3%, corneal opacities were found in 16.7% (6 patients with MPS I, II, VI and III), progressive increase in intraocular pressure was found in 5.6% (One patient with MPS I), while fundus examination showed early optic atrophy in 5.6% of patients (One patient with MPS II), bilateral papilloedema in 11.1% of patients (Two patients with MPS VI) and pigmentray retinopathy in 5.6% of patients (One patient with MPS III).

In the current study, mental retardation was found in patients with MPS IH, IHS, II and III while normal intellect was a feature of patients with MPS type IV and VI. The foregoing finding is in accordance with the statements of Neufeld and Muenzer[1] that profound mental retardation is a characteristic feature of MPS IH, the severe form of MPS II, and all subtypes of MPS III but normal intelligence may be retained in other types.

In the current study, heart affection was found in 40% of patients {patients with MPS I (25%), VI (10%) II (5%) and III (5%)} in the form of mitral prolapse and regurge. Shawky et al.[8] reported that cardiac manifestations were found in 11 patients of their studied cases (61.1%), the mitral valve was the commonest affected valve; (38.9% had

thickened mitral valve and 33.3% had mitral regurge), pulmonary hypertension was found in patients with MPS III (11.1%), coronary narrowing in patients with MPS I and IV (11.1%).

In MPS there is a wide spread described skeletal deformities which are typically referred to as dysostosis multiplex.[12] These include large skull with J shaped sella turicca, spatula shaped ribs, beaking of upper lumbar and lower thoracic vertebrae and pelvic dysplasia.[2] Skeletal deformities recorded among enrolled cases in the current study included deformities of vertebral column, thoracic cage and joints. Vertebral column involvement was in the form of lumbar kyphosis in 50% and kyphoscoliosis in 10% while straight veretebral columen was detected in 40% especially in those with type III, IS. Shawky et al.[8] found that kyphosis was the commonest vertebral column deformity as it was recorded in 45.9% of their cases while scoliosis was found in only 4.9% of them.

As regards joints involvement, 60% of cases had stiff joints, while 30% had normal joints and 10% who were diagnosed as cases of Morquio syndrome had lax joints. Mckusick et al.[13] stated that many joints of patients with Morquio syndrome, tend to be excessively loose.

The thoracic cage deformities mostly related to the sternum were found in 25% of enrolled cases in the current study. They were markedly a prominent feature in cases of Morquio syndrome. Such deformities were not present in cases with Hunter and Sanfilippo syndromes and this goes with Benson and Fenson[14], as they reported thoracic cage abnormalities in 50% of their cases with IH, IHS and IV types of MPS.

On the other hand, 15 out of 20 cases enrolled in the current study had hepatomegaly (75%), 11 cases had splenomegaly (55%) while umbilical and inginual hernias of variable severity were detected in 8 cases (40%) and 4 cases (20%), respectively. For comparison Shawky et al.[8] found hepatomegaly in 67.2% and splenomegaly in 37.7%.

In the present study the patients were subjected to estimation of the level of urinary GAGs by DMB test which proved to be high in all cases except one case suspected to be MPS IV and another case suspected to be MPS III.

After that patients were subjected to 2-DEP to determine the pattern of GAGs for probable type of MPS. Eleven cases (55%) showed dermatan sulfate (Type I, II, VI). The 7 cases (35%) showed hepran sulphate (Type III) while 2 cases (10%) showed keratan sulfate (Type IV). Finally patients were subjected to enzyme assay specific for each type. Patients who showed dermatan sulphate electrophoretic pattern by 2-DEP the α-L-iduronidase enzyme assay was done for them, 6 of them showed deficiency of the enzyme which is specific for MPSI (IH, IHS, IS). The two males with coarse facies,clear cornea and mental retardation, enzyme assay of iduronate-2-sulphate which is specific for MPS II was done for them and showed 0.1 and zero level. The rest of cases were subjected to Aryl sulfatase B assay specific for MPS VI

which showed zero level. The 7 patients who showed hepran sulfate which is specific for MPS III were subjected to the available enzyme assay in our laboratory for MPS III B (N-Acetyl-α-glucosaminidase) and their level ranged from 25-41.88 (Normal range 10-45μ mol/L/h), so these 3 patients with MPS III belong most probably to type III A, C, D where the deficient enzymes cannot be assayed in our laboratory. The 2 cases with characteristic skeletal deformity and showed keratan sulfate with 2-DEP were subjected to assay of galactose-6-sulphatase which is specific for MPS IV A which showed a low level .

Prenatal diagnosis was done by 2-DEP of the amniotic fluid for four mothers of affected patients of MPS. One fetus proved to be affected with MPS III. Another fetus was affected with MPS II. The other fetuses were normal.

In conclusion, definitive laboratory diagnosis of MPS is achieved by 3 sequential steps, which are the quantitative detection of excessive excretion of GAGs in the urine followed by urinary GAGs qualitative assay by two dimensional electrophoresis (2-DEP) to determine possible MPS type, the electrophoretic pattern of GAGs may be dermatan sulphate, heparan sulphate, and or keratan sulphate.

Heparan sulfate is diagnostic for MPS III. Dermatan sulfate pattern is present in MPS VI. In cases with MPS I (IH, IHS, IS) or MPS II, the electrophoretic pattern of GAGs may be a big dermatan sulfate spot figure (3).

So in cases of MPS I, II, VI the 2-DEP is not diagnostic for any of the 3 types. When one of these three types is suspected, it is recommended first to carry out an enzymatic assay for α-L-iduronidase. If it is deficient it is diagnostic for MPS I (IH, IHS, IS), but if it is of normal level, we are left with two other possibilities: first if the patient is a male, has clear cornea, and from family history there is an indication of X-linked recessive inheritance, it is recommended to conduct an assay of the enzyme iduronate-2-sulfatase, if it is deficient it is diagnostic for MPS II. The second possibility if the patient is either a male or a female with coarse facial features, gross corneal opacity, skeletal deformity, and organomegaly, it is recommended to do the enzymatic assay for aryl sulfatase B, if it is found to be deficient, it is diagnostic for MPS VI.

In cases of MPS IV, patients have characteristic skeletal deformities (Pectus craniatum, lumbar kyphosis, enlarged joints, lax joints, and receded head to the back), it is recommended to do enzymatic assay for both types of MPS IV (Severe and mild) from the start to avoid misdiagnosis of MPS IV as the patient may have a normal GAGs level and may be non excretory of keratan sulphate.

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