Review of Mucopolysaccharidosis Diseases at the Queen Sirikit National Institute of Child Health in the Past 15 Years

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Background: *Mucopolysaccharidosis (MPS) can be classified into 7 types according to the enzyme defects. Several countries use enzyme replacement therapy (ERT) as treatment for types 1, 2 and 6. ERT is very expensive: - therefore, to determine if this treatment could be made available in Thailand, it is important to know the numbers of the patients with MPS.*
Objectives: *To investigate the number and clinical profiles of MPS patients who visited the Queen Sirikit National Institute of Child Health (QSNICH) to determine the incidence of MPS in Thailand.*
Material and Method: *Review of MPS patients' medical records with confirmed diagnosis by enzyme tests, who visited QSNICH from January 1999 to December 2013.*
Results: *Medical records showed that 22 MPS patients visited QSNICH during the past 15 years. Of these patients, 5 were MPS 1 patients (intermediate type or Hurler-Scheie syndrome), 8 were MPS2 patients (severe form), 1 was a MPS3 patient, 2 were MPS4 patients and 6 were MPS6 patients (severe form). The first clinical sign observed in MPS1 is joint contracture, whereas in MPS2 is delayed development. For MPS2, all except one patient had macrocephaly (head circumference is more than 90 percentile). Other growth parameters, including weight and height, in MPS2 patients were higher than average (>50 percentile).*
Conclusion: *MPS2 is the most common type of MPS in this study, followed by type 6 and 1. The difference in growth parameters seen in MPS2 suggest that it may be a factor in the development of MPS2.*

Keywords: *Enzyme replacement therapy, Hunter syndrome, Hurler syndrome, Incidence, Maroteaux-lamy syndrome, Mucopolysaccharidosis, Overgrowth*

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Mucopolysaccharidosis (MPS) is a lysosomal storage disease. MPS can be divided into seven types, namely, type 1 (Hurler syndrome), type 2 (Hunter syndrome), type 3 (Sanfilippo syndrome), type 4 (Morquio syndrome), type 6 (Maroteaux-Lamy syndrome), type 7 (Sly syndrome) and type 9. All except type 2 are inherited as an autosomal recessive manner. In each type, patients do not have enough specific enzymes to digest mucopolysaccharide resulting in its accumulation and the gradual progressive damage of multiple organs. There are two forms of MPS type 1: severe form (Hurler syndrome) and attenuated form (Hurler-Scheie and Scheie syndrome)[1]. MPS type 2 or Hunter syndrome is the only type of MPS that shows X-linked recessive inheritance. Several symptoms of MPS2 are similar to MPS1 with the exception of cloudy cornea, which can be seen in MPS1 and not MPS2. Sanfilippo syndrome or MPS type 3 patients present with neurobehavioral problems. Somatic presentation of MPS3 is not as prominent as the other types. MPS4 (Morquio syndrome) patients have predominant problems in the skeletal system. MPS6 (Maroteaux-Lamy syndrome) patients share similar clinical presentation as Hurler syndrome in MPS1.

Enzyme tests are required to confirm the diagnosis of MPS. In the past years, enzyme replacement therapy (ERT) for the treatment of MPS1, MPS2 and MPS6 have been used in MPS patients around the world. The disadvantage of ERT is the high cost of the drug and is still a debated issue in the treatment of MPS in many countries[2-4].

To date, the incidence of MPS in Thailand has not yet been published. Due to the high cost of ERT, there is a need to know the number of patients with MPS to determine if the budget for ERT would be available in Thailand. Queen Sirikit National Institute

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of Child Health (QSNICH) is the leading hospital in Thailand specializing in child health and is suitable in representing MPS cases in Thailand.

Objectives

To investigate the number and clinical profiles of MPS patients who visited QSNICH to determine the incidence of MPS in Thailand.

Material and Method

Medical records of MPS patients who visited QSNICH during January 1999 to December 2013 were reviewed with approval from the patients and their families. Only MPS patients with confirmed diagnosis by enzyme tests were included into this study. MPS patients who were diagnosed by only clinical presentation without enzyme test were excluded from the present study.

Statistical analysis

Results are shown as percentages.

Results

Twenty-two MPS patients met the inclusion criteria for this study (MPS1 = 5 cases, MPS2 = 8 cases, MPS3 = 1 case, MPS4 = 2 cases and MPS6 = 6 cases). The proportion of each type was compared to other countries[5-8] and is shown in Table 1. The most common type of MPS in this study was MPS2 or Hunter syndrome, followed by type 6 and 1.

Results showed that sex ratio was almost equal in MPS type 1. All of MPS2 and MPS6 were male. Clinical presentation and symptoms of the MPS patients are shown in Table 2. The onset of symptoms is in range from birth to 4 years (Table 2). For MPS1, all patients were classified to have the attenuated form because of mild to moderate symptoms and normal development. All of MPS2 and MPS6 patients have severe form of the diseases because of the early onset and severe clinical symptoms. Joint contracture was the first sign observed in MPS1, whereas delayed development was the first sign in MPS2. For MPS2, all except one patient had macrocephaly (head circumference is more than 90 percentile). Other growth parameters, including weight and height, tend to be higher than average (>50 percentile). Consanguinity was found in 50% of MPS type 1, 3, 4 and 6 patients. Cloudy cornea was found in all MPS1, 4 and 6 patients. Mitral valve prolapse was found in almost every MPS patient (5 out of 6) who had undergone echocardiography. Common surgeries undergone by MPS patients were tonsillectomy, adenoidectomy (2 from 22 patients) and inguinal hernia repaired (5 from 22 patients).

Discussion

In the past 10 years, only MPS1 and 2 enzyme tests were available in Thailand. Other types of MPS were diagnosed with a special test-urine thin layer chromatography-that is less sensitive and specific than the enzyme tests. This could result in the inaccuracy on the incidence of MPS patients. In the later 5 years (from 2009-2013), more enzyme tests were available, including test for the diagnosis of MPS3, 4, 6 and 7. Many patients, including the past patients confirmed their diagnosis by these enzyme tests. This could result in the increased number of MPS patients over the last 10 years.

Despite the availability of enzyme tests, the number of MPS patients is still not accurately identified. This may be due to the less pronounced somatic phenotype in some subtypes of MPS, the rarity of MPS cases, and the unawareness of MPS diseases. To accurately determine the incidence of MPS diseases, newborn screening should be made available in Thailand as done in other countries[9,10].

The proportion of MPS types in the present study is different from studies done in other countries. The most common type of MPS is MPS2 which is consistent with the study performed in Taiwan. On the other hand, Western countries have low incidence of MPS2 as shown in Table 1. This study showed that MPS1 and 6 is the second and third most common type after MPS2, which is different from the study in Taiwan.

Table 1. Proportion (in percentage) of the MPS patients by subtype in each country

Country	MPS1	MPS2	MPS3	MPS4	MPS6
Taiwan[5]	5	52	29	26	7
Northern Ireland[6]	41	17	9	32	0
Germany[7]	20	18	45	11	7
Western Australia[8]	27	9	50	5	9
Present study (QSNICH)	23	36	5	9	27

Table 2. Characteristics of 22 MPS patients

Patient	Sex	Type of MPS	Onset (Year)	Symptoms	Diagnosis (Year)	Weight (% tile)	Height (% tile)	HC (% tile)	Development	Eye	Echo	Surgery
1	Male	1	2	Joint stiffness	3.5	10-25	<3	10-25	Normal	Cloudy	N/A	T&A at 8 years old
2	Male	1	2	Joint stiffness	4.5	25-50	50-75	97	IQ =90	Cloudy	MVP	
3	Male	1	2.5	Joint stiffness	4	<3	<3	25	Normal	Cloudy	MVP	Inguinal hernia at 6 years old
4	Female	1	1.5	Knock knee	2.5	25	50	75	IQ =90	Cloudy	N/A	
5	Female	1	3	Joint stiffness	5	75	75	97	IQ = 95	Cloudy	N/A	
6	Male	2	3	Delay speech	4	>97	50-70	>97	Delayed	Clear	N/A	
7	Male	2	0.5	Inguinal hernia	4	50	25	>97	Delayed	Clear	Cardio-myopathy	Inguinal hernia at 6 months old, T&A at 6 years old
8	Male	2	0.5	Chronic rhinitis	2	>97	>97	>97	Delayed	Clear	MVP	
9	Male	2	2	Delayed speech	4	75	25	>97	Delayed	Clear	N/A	
10	Male	2	3	Joint stiffness	8	75	50-75	90	IQ =59	Clear	N/A	
11	Male	2	1.5	Autism	7	50	50	97	Delayed	Clear	MVP	
12	Male	2	1	Delayed speech	3	>97	50	>97	Delayed	Clear	N/A	Inguinal hernia at 1 year old
13	Male	2	1	Snoring	2.5	90	50	50-75	Delayed	Clear	N/A	
14	Female	3	4	ADHD	14	<3	<3	>97	Regression	Clear	N/A	
15	Female	4	3	Short stature	4	10	<3	50	Normal	Cloudy	N/A	
16	Female	4	5	Short stature	7	10-25	<3	97	Normal	Cloudy	N/A	
17	Male	6	1.5	Kyphosis	2	50	50	90-97	Normal	Cloudy	N/A	Inguinal hernia at 3 year old
18	Male	6	birth	Kyphosis	1.5	50	10-25	97	Normal	Cloudy	N/A	
19	Male	6	4	Dysmorphic	4	10-25	<3	50	Normal	Cloudy	MVP	Inguinal hernia at 3 year old
20	Male	6	1.5	Dysmorphic	1.5	10-25	<3	50	Normal	Cloudy	N/A	
21	Male	6	1.5	Dysmorphic	1.5	50-75	50-75	50-75	Normal	Cloudy	N/A	
22	Male	6	3	Macrocephaly	3.5	10	<3	0.5	Normal	Cloudy	N/A	

HC = head circumference; T&A = tonsillectomy and adenoidectomy; MVP = Mitral valave prolapse; N/A = not available

The difference could be due to the sample size. The interesting issue in the study population is MPS6 that is common as well as MPS1. The proportion of MPS6 is the highest in other studies. All MPS6 patients in the present study had severe symptoms of early onset from birth to 4 years, and significant symptoms such as dysmorphic or short stature. The rapid disease progression in MPS6, which is the common type of MPS6 in Asian countries[11], and coarse faces, which is pronounced in MPS6 but not in MPS1 and 2, leads to early identification of cases and may affect the proportion of MPS in the present study.

For MPS1, joint contracture at age of 2-3 years was the chief complaint leading patients to the orthopedic department, except in one case where the patient presented with knock-knees at 1.5 years of age. Coarse face was not a predominant symptom in any of patients before the age of 5. All of the patients had normal development. This suggests that they are more likely to have the attenuated form of MPS1 (Hurler-Scheie syndrome).

All of MPS2 patients in the present study had the severe form, not the attenuated form as seen in MPS1. The first symptom is delayed development seen in 50% of the cases. Patients also had other non-specific clues such as snoring, chronic rhinitis or joint contracture which is not uncommon in MPS2. Another clue leading to the diagnosis is growth parameters. All except one patient had macrocephaly (head circumference is more than 90 percentile). Half of the patients weighed at the 90 or >97 percentile. The other half of the MPS2 patients weighed at the 50-75 percentiles. Six out of 8 MPS2 patients' height was at 50 or higher. One patient was diagnosed with overgrowth syndrome for some years before being accurately diagnosed with MPS2. This suggested that overgrowth might be another clue for MPS2.

For the one MPS3 patient, it took almost 10 years to make a diagnosis because the patient only presented with neurobehavioral problems at the time. Dysmorphism or other organ involvement was subtle. This suggests that the number of MPS3 patients in the study may not be as accurate due to under recognition of the disease.

For MPS4, the patients presented at the orthopedic department with significant bone deformity and no coarse face. The number of patients with MPS4 in this study is significantly lower than the studies done in other countries (Table 1). This may be due to lack of knowledge and unawareness of MPS4. Screening of MPS4 should be done in orthopedic patients with bilateral dysplastic hip disease and/or spondyloepiphyseal, which are recognized presenting symptoms for MPS diseases[13].

Interestingly, all of MPS6 patients were male as it is inherited as an autosomal recessive trait. Their chief complaints from patients were either bone abnormality (kyphosis) or dysmorphic face. The patients were classified as having the severe form of MPS6 because of their early onset and severe symptoms.

All of MPS1, 4 and 6 patients had the typical sign of cloudy cornea. None of MPS2 patients had cloudy cornea, which is the differential diagnosis for MPS2. The common cardiac finding in MPS is mitral valve prolapse, which was found in every case of this study except one that had undergone echocardiography. There was one MPS2 patient that had cardiomyopathy and no mitral valve prolapse. Cardiac involvement is common in MPS. All MPS patients are required to have echocardiography examination as a part of the disease management. Unfortunately, the other 16 patients did not undergo echocardiography due to the limitation of resources. Common surgeries in MPS are adenotonsillectomy and inguinal hernia repair[12]. Five out of 22 cases in the present study had inguinal hernia surgery. Therefore, MPS may need to be ruled out in any patient who comes for inguinal hernia repaired.

Conclusion

Hunter syndrome or MPS2 (severe form) is the most common type among other MPS types in this study. MPS6 (severe form) and MPS1 (attenuated form) are less common but the summation of these two subtypes accounts for 50% of all MPS cases. Joint contracture is the first presenting sign in MPS1 whereas delayed development is the first sign in MPS2. Coarse face is less common in these two subtypes of MPS. Other growth parameters, including weight and height, in MPS2 patients, are higher than average (>50 percentile) suggesting that overgrowth may be another clue for MPS2.

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Potential conflicts of interest

None.

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การศึกษาผู้ป่วยกลุ่มโรคมิวโคโพลีแซคคารายด์โดสิสในสถาบันสุขภาพเด็กแห่งชาติมหาราชินีย้อนหลัง 15 ปี

จุฬาลักษณ์ คุปตานนท์, สุทธิพงษ์ ปังคานนท์

ภูมิหลัง: *กลุ่มโรคมิวโคโพลีแซคคารายด์โดซิสแบ่งออกเป็น 7 ชนิดตามเอนไซม์ที่บกพร่อง ปัจจุบันในหลายประเทศมีการรักษาด้วยการให้ยาเอนไซม์ทดแทนเอนไซม์ที่บกพร่องในโรคชนิดที่ 1, 2 และ 6 แต่ยานี้มีราคาแพงมาก การพิจารณาใช้ยาชนิดนี้ในประเทศไทยจึงจำเป็นต้องรู้จำนวนผู้ป่วยในแต่ละชนิดในโรคกลุ่มนี้*

วัตถุประสงค์: *เพื่อศึกษาถึงจำนวนและอาการทางคลินิกของผู้ป่วยกลุ่มโรคมิวโคโพลีแซคคารายด์โดซิสแต่ละชนิด เนื่องจากอุบัติการณ์ของโรคนี้ยังไม่ทราบ*

วัสดุและวิธีการ: *ได้ทบทวนเวชระเบียนของผู้ป่วยกลุ่มโรคมิวโคโพลีแซคคารายด์โดซิสแต่ละชนิดที่มารับการรักษา ที่สถาบันสุขภาพเด็กแห่งชาติมหาราชินี ตั้งแต่ เดือนมกราคม พ.ศ. 2542 ถึง เดือนธันวาคม พ.ศ. 2556*

ผลการศึกษา: *มีผู้ป่วยกลุ่มโรคมิวโคโพลีแซคคารายด์โดซิส 22 รายในช่วงระยะเวลา 15 ปี เป็นชนิดที่ 1, 2, 3, 4 และ 6 จำนวน 5, 8, 1, 2 และ 6 รายตามลำดับ อาการข้อติดเป็นอาการแรกที่นำผู้ป่วยชนิดที่ 1 มารับการรักษา ในขณะที่พัฒนาการช้าเป็นอาการสำคัญของผู้ป่วยชนิดที่ 2 ในผู้ป่วยชนิดที่ 2 ยังพบว่าผู้ป่วยทุกคนยกเว้น 1 รายมี ศีรษะที่โต (90 ถึง >97 เปอร์เซ็นต์ไทล์) การเจริญเติบโตในด้านความสูงและน้ำหนักก็มากกว่าค่าเฉลี่ยทั่วไปของเด็กปกติ (>50 เปอร์เซ็นต์ไทล์)*

สรุป: *ผู้ป่วยกลุ่มโรคมิวโคโพลีแซคคารายด์โดซิสชนิดที่ 2 มีความชุกมากที่สุด รองลงมาคือชนิดที่ 6 และ 1 ตามลำดับ การเจริญเติบโตในด้านต่างๆ อาจเป็นตัวชี้แนะหนึ่งในกลุ่มโรคมิวโคโพลีแซคคารายด์โดซิสชนิดที่ 2*