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□ Original Article : Clinical Study □

Clinical and Laboratory Features of Korean Mucopolysaccharidoses (MPSs)

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Purpose : The mucopolysaccharidoses (MPSs) are a heterogeneous group of lysosomal storage disorders. They are caused by a deficiency of the enzymes involved in the degradation of glycosaminoglycans. Early recognition is important because recombinant enzyme replacement therapy is now available for MPS. We studied the clinical characteristics of 80 MPS children with the object of determining the epidemiological, clinical and radiological features in Korean MPS children.

Methods : Diagnosis of MPS was confirmed by skin fibroblast enzyme analysis in 80 patients between February 1995 and December 2004. Charts were retrospectively reviewed for clinical and radiological findings, as well as for intelligence and speech evaluations.

Results : Hunter syndrome (MPS type II) was the most prevalent type, appearing in 51/80 cases (64 %), followed by Sanfilippo syndrome (MPS III-18%), Hurler syndrome (MPS I-15%), and Morquio syndrome (MPS IV-4%). The average age at diagnosis was 5.5 years (range 1 to 20), and the male-to-female ratio was 4.7 : 1. Typical radiographic changes were observed in 45/54 cases (83%). Mitral regurgitation was the most common cardiac defect. Moderate to profound mental retardation and hearing loss were present in 14/35 cases (56%) and 33/38 cases (82%), respectively. Four MPS II patients had bone marrow transplantation, with mixed outcomes. Five MPS I patients are currently on enzyme replacement therapy.

Conclusion : Our study showed a high proportion of MPS II cases (64%), which may represent population variability. By studying the clinical features of these patients, we hope to alert pediatricians of the warning signs of MPS. **(Korean J Pediatr 2005;48:1132-1138)**

Key Words : Mucopolysaccharidoses, Clinical, Laboratory, Incidence, Korea

Introduction

Mucopolysaccharises (MPSs) are inherited lysosmal storage diseases caused by lysosomal hydrolase deficiencies that disrupt the catabolism of glucosaminoglycans (GAG). The pattern of inheritance is generally autosomal recessive, except for MPSII, which is X-linked[1]. The incidence of MPS may be as high as 1 in 29,000 live births. Hurler syndrome is reported as the most frequently occurring type in western countries[2-4], whereas Hunter syndrome is more prevalent in Israel[5], Japan, and Korea.

There are at least 10 enzymes known to be required for the stepwise degradation of dermatan sulfate, heparan sulfate, keratan sulfate, and chondroitin sulfate. Deficiencies of these enzymes lead to a lysosomal accumulation of GAGs which eventually leads to multi-organ dysfunction. At birth, these patients are phenotypically normal, but they gradually develop morphologic changes such as coarse faces, hepatosplenomegaly, and dystosis multiplex. Other symptoms including recurrent respiratory infections, joint stiffness, cardiac problems, and mental deterioration can also occur[1, 6-9]. Eleven known enzyme deficiencies can give rise to seven distinct types of MPS. There is clinical similarity among the different enzyme deficiencies, and conversely, a wide spectrum of clinical severity within any enzyme deficiency[1, 6-10].

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Treatment of MPS is difficult. Bone marrow transplantation has been partially successful in increasing the life expectancy and decreasing systemic abnormalities in selected patients with the severe forms of MPS I, MPS II, and MPS IV[11-14]. Recently, enzyme replacement therapy has been shown to be a promising method to reduce GAG accumulation in some organs[15-17].

Over 80 patients are enrolled in the Samsung Medical Center MPS Clinic, the largest clinic of its kind in Korea. The object of this study was to better understand the clinical features of Korean MPS children by studying the clinical and radiographical findings of 80 patients diagnosed with MPS at the Samsung Medical Center.

Materials and Methods

Eighty patients with different forms of MPS were identified between February 1995 and December 2004. In every patient, the diagnosis was confirmed by an enzymatic activity assay of skin fibroblasts. Charts were retrospectively reviewed for clinical features such as age at diagnosis, sex, family history and previous medical history. Findings on physical examination were obtained from the physician's note on admission. Eighty patients were evaluated according to our hospital's MPS evaluation protocol, which includes simple chest X-rays, a radiological skeletal survey, a brain MRI, an abdominal CT, echocardiography and nerve conduction velocity testing. An ophthalmologic evaluation was performed by an ophthalmologist to screen for any corneal opacity. Otolaryngologic evaluations included examinations of the airway and the tympanic membranes, as well as hearing tests. Speech was evaluated using a Preschool Language Scale (PLS) or skills in communication-revised. A speech delay of less than six months for the person's age was defined as mild, while a delay of more than 12 months was called moderate. A delay of more than 24 months was identified as severe. The evaluation of intelligence was performed by using the Development Institute's-Wechsler Intelligence Scale for Children (KEDI-WISC) for children over six years of age. In younger or uncooperative children, a developmental test of visuomotor integration or social maturation was used. Profound mental retardation was defined as a social score of less than 25, while a score of 25-35 represented severe mental retardation. Those scoring 35-50 were labeled as moderately retarded, while those in the 50-70 range had mild mental retardation. A social score over 70 was classified as normal mental ability.

For confirmative diagnoses, fibroblast cultures from skin biopsies were sent to the Lysosomal Storage Disease research unit of the Women and Children's Hospital in Australia.

Results

1. Patient classification

Eighty cases were classified as follows : MPS I 12/80 cases (15%), MPS II 51/80 cases (64%), MPS III 14/80 (18%), and MPS IV 3/80 cases (4%) (Table 1). The average age at diagnosis was 5.5 years (ranging from 1 to 20 years). The male-to-female ratio was 4.7 : 1. All Type II patients were male. A family history of MPS in siblings, cousins, uncles, or an unexplained death in a family member was observed in 27 cases (33%). During this period three MPS I patients, five MPS II patients and two MPS

Table 1. Classification and Clinical Features of Mucopolysaccharidoses

Classification	Number	Age of onset	Sex ratio (M/F)	Family Hx	Expire
Type I	12(15)	6.8	7/5	3	3
HurlerType	4(5)				
ScheieType	5(6)				
Huler-Scheie	3(4)				
Type II	51(64)	5.1	51/0	22	5
Mild	18(23)				
Severe	33(41)				
Type III	14(18)	5.6	8/6	2	2
A	5(6)				
B	7(9)				
Unclassified	2(3)			–	–
Type IV	3(4)	7.7	–/3	27	7
Total	80	5.5	66/14		

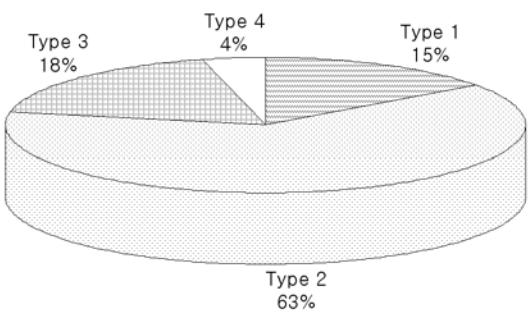

Fig. 1. The frequency of patients by mucopolysaccharidoses type.

III patients died (Fig. 1).

2. Presenting symptoms

Most patients had uneventful birth histories. Eighty-five percent were born at term, with birth weights appropriate for their gestational ages. Five patients were born before 37 weeks gestation, and only two of these patients were hospitalized in the newborn period. Causes for this early hospitalization were meconium aspiration for one patient and prematurity for the other. All other patients appeared normal at birth. Sixteen parents (23%) reported that delayed development was their first clue that their child was not progressing normally. Others reported delayed speech (17%), coarsening facial features (16%) and joint stiffness (14%). These results are presented in Table 2.

Table 2. Presenting Features of Mucopolysaccharidoses

Parental reported first sign	(n=70)	Percentage (%)
Developmental delay	16	23
Decreased joint range of motions	10	14
Progressive coarsening of facial features	11	16
Loss of developmental skills such as speech	12	17
Mental deterioration	2	3
Lumbar kyphosis	3	4
Unusual gait	4	6
Protruding abdomen due to hepatosplenomegaly	1	1
Short stature	2	3
Corneal opacity	1	1
Frequent URI	6	9
Others	2	3

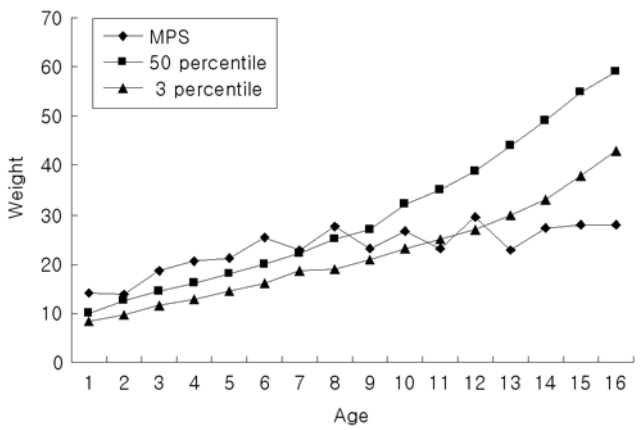

Fig. 2. Average weight of MPS patients compared to growth curve of general population.

3. Growth and Development

Growth curves showed decreased linear growth in the postnatal onset pathologic short stature patterns. Growth parameters were normal or increased through infancy, and then they decreased dramatically in middle childhood (Fig. 2). By 5-10 years, patients' weights and heights fell below the third percentile for age in 11% and 44%, respectively. By 10 years, body weight was below the third percentile for age in 80%, and height was less than the third percentile in 100% (Table 3).

4. Clinical Course

The frequency of seizures in patients was 20%. In five cases, an obstructive airway severe enough to require tracheostomy was observed, while umbilical or inguinal herniorrhaphy was performed in 25 cases. Percutaneous endoscopic-guided gastrostomy (PEG) had been done on six patients, and another six patients were hospitalized for pneumonia, with one patient having 11 recurrent episodes.

5. Radiographic findings in skeletal survey

Skeletal abnormalities were evident in 45 out of 54 cases that were radiologically studied (83%). We found the following radiographic findings : canoe paddle appearance of ribs (59%), thick and short clavicles (50%), anterior inferior breaking of spine (59%), kyphosis or scoliosis (37%), posterior scalloping (20%), flaring of the iliac wing (56%), coxa valga (21%), thick and short phalanx (52%), and medially-tilted radius and ulna (30%). These results are shown in Table 4.

6. Brain MRI findings

Among the 47 patients in whom brain MRI was per-

Table 3. Distribution of Height and Weight of Mucopolysaccaridoses Patients by Age

Percentile for age	Weight			Height		
	<5 yr (n=25)	5-10 yr (n=44)	>10 yr (n=10)	<5 yr (n=24)	5-10 yr (n=34)	>10 yr (n=7)
>97	8	6	-	2	2	-
90-97	2	5	-	4	-	-
75-90	7	5	-	3	1	-
50-75	5	6	-	8	1	-
25-50	1	3	2	4	5	-
10-25	2	6	-	-	9	-
23-10	-	3	-	1	5	-
<3	-	5(11%)	8(80%)	2(8%)	11(46%)	7(100%)

Table 4. Radiographic Findings on Skeletal Survey

	I(n=9)	II(n=39)	III(n=4)	IV(n=2)	Total(n=54)
Chest					
Canoe paddle appearance of ribs	8	21	2	1	32(59)
Thick and short clavicle	7	17	2	1	27(50)
Narrowing of trachea	−	2	−	−	2(4)
Spine					
Anterioinferior breaking of spine	4	24	3	1	32(59)
Kyphosis or scoliosis	4	14	−	2	20(37)
Posterior scalloping	3	8	−	−	11(20)
Atlantoaxial subluxation	1	−	−	−	1(2)
Pelvis					
Flaring of the iliac wing with narrowing of distal part of ilium	6	22	2	−	30(56)
Coxa valga	3	8	−	−	11(21)
Narrowing of femoral head	1	4	1	−	6(11)
Hand					
Thick and short trapezoidal phalanx with widening of diaphysis	4	21	3	−	28(52)
Distal ulna radius tilted medially	3	11	2	−	16(30)
Osteopenia	1	2	−	−	3(6)
Dystosis multiplex	9	31	4	1	45(83)

Table 5. Brain MRI Findings

Findings	I(n=8)	II(n=30)	III(n=8)	IV(n=1)	Total(n=47)
Ill defined high signal intensity lesions on PVWM	6	21	−	−	27(57)
Prominent perivascular spaces	5	10	1	−	16(34)
Extra-axial CSF space widening	2	5	2	−	9(19)
Ventriculomegaly	2	12	4	−	18(38)
Diffuse brain atrophy	1	10	6	−	17(36)
Multiple small cystic lesion	2	10	−	−	12(25)
Meningocele or megacisterna magna	1	2	−	−	3(6)
J shaped sella turcica	1	6	2	−	9(19)
Spinal cord compression	1	1	1	−	3(6)
Normal	−	−	−	1	1(2)

Table 6. Echocardiographic Findings

Echo	MPS I	MPS II	MPS III	MPS IV	Total (%)
Mitral valve thickening	10	31	4	1	46(82)
Mitral regurgitation	4	23	3	1	31(55)
Mitral stenosis	1	3	−	−	4(7)
Aortic valve thickening	6	28	−	−	34(61)
Aortic regurgitation	1	5	−	−	6(11)
Aortic stenosis	3	6	−	−	9(16)
Left ventricle hypertrophy	1	6	−	−	7(13)
Mitral valve prolapse	5	9	2	−	16(29)
Sinotubular junction narrowing	−	2	−	−	2(4)
Normal	−	1	−	1	2(4)
Total	10	40	4	2	56

formed, all but one had abnormal findings. The most common changes were : poorly defined high signal intensity (57 %), ventriculomegaly (38%), diffuse brain atrophy (36%), prominent perivascular spaces (34%), and multiple small cystic lesions (25%). See Table 5 for these statistics.

7. Abdominal CT

An abdominal CT was performed in 40 cases. Common findings were : hepatosplenomegaly (73%), hepatomegaly (15 %), and umbilical hernia.

8. Echocardiographic findings

Cardiac abnormalities were observed in 54 cases (96%). The mitral valve was the most commonly affected valve; 82% had thickened mitral valves, 55% had mitral regurgitation, and 29% had mitral valve prolapse. Aortic valve thickening was observed in 61%, and aortic stenosis was seen in 16%. Aortic regurgitation was found in 11% (Table 6).

9. Nerve conduction velocity (NCV)

Among the 35 patients in whom an NCV study was performed, 25 patients (71%) had abnormalities of the median nerve conduction. Three of these patients had only sensory losses while two had only motor losses, and a total of 20 patients had both motor and sensory losses.

10. Ophthalmologic examination

Corneal opacity was evident in 13/46 (28%) patients, while a fundus examination revealed optic disc swelling in one patient. The frequency of corneal opacity was highest in Type I patients at 70%.

11. Otolaryngologic examination

Sixty-three patients received otolaryngologic examinations. Middle ear effusion (MEE) was observed in 46/63 cases (73%), a V-tube was inserted in 28/63 cases (44%), and a tonsillectomy and adenoidectomy was performed in 13 cases (21%).

The average ABR threshold was 64 dB with the highest average appearing in Type II patients (66.9 dB), and the lowest seen in patients with Type IV (20 dB). Hearing loss occurred in 87% and severe to profound hearing loss was found in 68% of the patients (Table 7).

Table 7. Otolaryngologic Findings

Finding	(n=63)	Percentage(%)
Middle ear effusion	46	73
V-tube	28	44
Tonsillectomy and adenoidectomy	13	21
Hearing loss	(n=38)	18
Moderate(ABR 35-50)	7	18
Severe(ABR 50-70)	13	34
Profound(ABR >70)	13	34
Total	33	87

Table 8. Intelligence and Speech Evaluation

	MPS I (n=6)	MPS II (n=24)	MPS III (n=5)	Total (n=35)
Social score				
Normal(>70)	5	9	−	14(40%)
Mild(50-70)	1	5	1	7(20%)
Moderate(35-50)	−	7	1	8(23%)
Severe(25-35)	−	−	1	1(3%)
Profound(<25)	−	3	2	5(14%)
Average IQ	87.2 (n=3)	62.2 (n=18)	32.2 (n=4)	62.2 (n=25)
Speech				
Normal	1	−	−	1(4%)
Mild(6-12 Mo delay)	−	1	−	1(4%)
Moderate(12-24 Mo delay)	−	5	−	5(20%)
Severe(>24 Mo delay)	2	12	4	18(72%)

12. Intelligence and speech evaluation

Intelligence examinations were performed on 35 Type I, II and III patients. The average IQ was 62.2, and the highest scores were seen in Type I patients (87.2). Of the 25 patients examined, 14 patients (40%) had normal intelligence, seven (20%) had mild mental retardation (MR), eight (23%) had moderate MR, and six (17%) had severe to profound MR.

Speech delay was observed in 24 of the 25 patients (96 %). A mild speech delay was seen in one (4%), a moderate delay in five (20%) and a severe delay in 18 cases (72 %). See Table 8 for a summary of these results.

Discussion

MPSs are a heterogeneous group of lysosomal storage disorders, each caused by a deficiency of an enzyme involved in the degradation of glycosaminoglycan. These enzyme deficiencies can lead to an accumulation of glycosaminoglycan in the lysosomes, which can result in cell, tissue, and organ dysfunction[1, 6-9].

The overall prevalence of the MPS disorders is difficult to estimate because of the small number of population-based studies. An epidemiologic study in Western Australia reported the incidence of MPS to be approximately 1 in 107,000 live births for MPS I, 1 in 58,000 for MPS II, 1 in 58,000 for MPS III, 1 in 640,000 for MPS IV A, and 1 in 230,000 for MPS VI. The overall incidence for all types of MPS was approximately 1 in 29,000 live births[3]. These estimates are in agreement with figures from British Columbia population studies[2]. MPS Type I is the most prevalent type in Caucasians[2-4], whereas MPS II is more common in people from Israel, Japan, and Korea[5]. Our results show a high proportion of MPS II cases (64%), which may represent population variability.

Our clinical investigation revealed short stature of less than third percentile for age in 44% of children above five years, and in all children older than 10 years. Dystosis multiplex, a term used to describe the array of radiographic skeletal findings including a thickened, large skull, paddle-like ribs, or an anterior breaking of the vertebral bodies, was observed in 45/54 cases (83%). Cardiac invol-

vement was found in 54 of the 55 cases evaluated (96%). The most common changes were abnormalities of the mitral and aortic valves. Hepatosplenomegaly was detected in 29/40 cases (73%). Twenty-five out of 35 cases (71%) had abnormal findings seen on NCV of the median nerve. Corneal opacity was observed in 13/46 cases (28%), and MEE in 46/63 cases (73%). Moderate to profound mental retardation was present in 56% of Type I to III. Intelligence was normal in all MPS IV patients and in 83% of MPS I patients.

Possible limitations of this study include the uneven distribution of patients in each subtype and a discrepancy in the number of subjects for each evaluation. Only 47 patients completed the full battery of studies, while others were excluded due to incompliance or other limiting circumstances. For example, evaluations of intelligence were executed in patients with better performance, and patients with poor cooperation were excluded from ophthalmic evaluations, while children unable to stand were not measured for height.

Until the early 1980s only palliative and nonspecific therapies were available for patients with an MPS disorder. This changed with the advent of bone marrow transplantation (BMT), which proved beneficial in selected cases of MPS I, MPS II and MPS IV[11-14]. Early transplantation in MPS I (before 24 months of age and any onset of neurological disease) can improve hearing, cardiac function, upper airway functioning, and linear growth, as well as reduce organomegaly and slow intellectual deterioration[11-14]. However, BMT did not significantly alter the development of musculoskeletal changes in MPS I[12, 19, 20].

From 1995 to 2004, four MPS II patients in this group had BMT from HLA-matched siblings. The mean age at BMT was 6.9 years (with a range of 2.8-15 years). Six months after BMT, all four children showed improvement of joint mobility as well as an improvement of the characteristic coarse facial features. One patient had improved hearing. However, seven months after BMT, one patient died from complications related to a graft vs. host reaction. The remaining three children were evaluated five years after BMT. One patient suffered from severe depression, and all three children required special education due to mental retardation. Thus, the outcome of BMT seems to depend on the timing of evaluation. The long-term outcome may not be as encouraging as was once hoped.

Recent clinical trials of enzyme replacement therapy have shown promise in the treatment of MPS I, MPS II and MPS IV, and enzyme replacement therapy recently became commercially available for MPS I[15-17]. Early treatment, before any development of irreversible damage, results in an improved outcome. Thus, it is imperative that physicians are aware of the warning signs and symptoms of MPS so that patients can be diagnosed and provided with up to date care. Currently, five MPS I patients in this group are being treated with enzyme replacement therapy. Although early results are promising, the long-term outcome remains to be established.

한 글 요 약

한국 뮤코 다당체 침착증 환자에 대한 임상적 고찰

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목 적 : 뮤코 다당체 침착증은 glycosaminoglycan을 분해하는 라이소솜 효소의 유전적 결핍에 의해 라이소솜에 전구 물질이 축적되는 질환군이다. 임상 양상은 매우 다양하지만, 일반적으로 만성적이고 진행되는 경과를 보이며 투박한 얼굴 모양, 관절의 경직, 간비 비대, 성장 지연, 신경학적 퇴화를 특징으로 한다. 최근 뮤코 다당체 침착증 I형의 효소 대체 요법이 가능하며 곧 II형에서도 실용화될 전망이다. 임상 증상이 나타나기 전에 효소 치료를 시작함으로써, 뮤코 다당체 침착증 환자에서 보이는 신경학적 및 근골격계 퇴행의 예방이 가능할 것으로 기대하고 있으며, 이에 조기 진단이 더욱 강조되고 있는 상황이다. 저자들은 본원 뮤코 다당체 침착증 환아 모임에 가입된 환아 80명을 대상으로 임상 양상을 분석하여, 국내 뮤코 다당체 환아들의 임상양상을 연구하고자 하였다.

방 법 : 1995년 2월부터 2004년 12월까지 삼성서울병원 소아과를 방문한 환아 중, 피부 섬유아세포 배양 효소 검사에 의해 뮤코 다당체 침착증이 확진된 환아 80명을 대상으로 하였다. 입원기록 및 외래기록을 검토하여 진단시 연령과 성별, 가족력, 이학적 특징, 방사선 검사, 이비인후과 검사, 안과 검사, 지능검사, 언어 평가에 대한 결과를 분석하였다.

결 론 : 유형별로 II형이 51명(64%), III형이 14명(17.5%), I형이 12명(15%), IV형이 3명(3.8%)으로 II형의 빈도가 월등히 높았다. 진단시 연령은 1세부터 20까지 있었으며, 평균 5.5세였다. 남녀비는 4.7:1이였고, II형 헌터 증후군 51명은 모두 남아였다. 부모가 환아에서 이상을 느낀 첫 징후는 발달 지연이 12례(17%)로 가장 많았고, 그 외에 언어 발달지연(17%), 외모의 이상(16%), 관절 경직(14%) 등이 있었다. 방사선 검사상 전형적인 골격계 변화가 45례(83%)에서 관찰되었다. 55례에서 심장 초음

파 검사를 시행했는데 판막의 비후와 경한 역류 소견이 많았고 특히 승모판막의 비후와 역류가 각각 46례(82%), 31례(55%)로 가장 빈번하였다. 이비인후과 평가를 받은 63례 중 46례(73%)에서 중이저류가 관찰되었고, 28례의 환아는 환기관 삽입을 시행받았다. 33례(82%)에서 중등도 이상의 청력소실이 있었고, 특히 II형 환아들의 ABR 역치 평균이 66.9로 가장 높았다. 지능검사가 가능했던 35례의 환아 중에서 중등도 이상의 정신 지체가 14례(56%)였다. II형 51례의 환아 중에서 4명이 HLA 일치되는 형제로부터 골수이식을 받았다. 그 중 1명은 이식편대 숙주 반응 합병증으로 사망하였고, 나머지 3명에서도 신경학적 퇴행을 예방하지 못하였다. 현재 5명의 I형 환아들에서 효소 대체 치료를 시작하였고 이들의 임상 경과를 주목하고 있다.

결 론 : 본 연구에서는 80명의 뮤코 다당체 침착증 환자를 대상으로 임상 양상을 분석하였고 유형별로는 II형 헌터 증후군의 빈도가 64%로 외국 연구에 비해 월등히 높았으며 이는 인구학적 차이를 반영한다고 사료된다. 발달 지연, 저신장, 근골격계 변화, 심장판막 변화, 정신 지체, 청력 소실 등 뮤코 다당체 침착증의 전형적인 증상들이 환아의 대부분에서 관찰되었다. 저자들은 국내 뮤코 다당체 침착증 환아들의 임상적 양상을 연구함으로써 조기 진단과 적절한 치료를 하는데 도움이 되고자 하였다.

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