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원 저

I형 뮤코다당증 환자들에서 효소 보충 요법이 성장에 미치는 영향

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Effect of Enzyme Replacement Therapy on Growth in Korean Patients with Mucopolysaccharidosis Type I

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Purpose: Mucopolysaccharidosis type I (MPS I) is a lysosomal storage disorder caused by deficiency of the enzyme α-L-iduronidase, which leads to a broad spectrum of multisystemic manifestations. Short stature and decreased growth velocity are prominent features of MPS I. The aim of the present study was to evaluate the effect of enzyme replacement therapy (ERT) on growth of Korean MPS I patients from a single center.

Methods: Height data were obtained by retrospective chart review of 10 Korean patients with MPS I who had received ERT for a minimum of 3 years. Height was expressed as standard deviation scores (SDS) based on normative data. Annual growth rates were calculated before and during ERT. A piecewise regression model was used to analyze height z-scores before and after treatment. Individual analysis was performed for impact of phenotype [(severe (Hurler) versus attenuated (Hurler-Scheie, Scheie)] on growth.

Results: Annual growth was 3.3 cm (z-score= -0.21) in the year before ERT and 6.2 cm (z-score= 0.17), 5.8 cm (z-score= 0.07), and 3.8 cm (z-score= -0.4) in the first, second, and third years of ERT, respectively. Regression analysis showed improvement in the slope after ERT (difference= 0.04; P=0.022). Estimated slope differences between severe and attenuated phenotypes were statistically significant before (P=0.001) and after treatment (P<0.0001), although no significant difference was noted when stratified by phenotype.

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Conclusion: ERT with aldurazyme appears to have a positive impact on linear growth in patients with MPS I.

Kew words: Mucopolysaccharidosis type I, Hurler, Scheie, Enzyme replacement therapy, Aldurazyme, Growth

Introduction

Mucopolysaccharidosis type I (MPS I) is an autosomal recessive lysosomal storage disorder caused by deficiency of the enzyme a-L-iduronidase (IDUA), which is responsible for degradation of the glycosaminoglycans (GAGs) dermatan sulfate and heparan sulfate within cells[1]. Lysosomal accumulation of GAGs leads to a chronic, multisystemic disease characterized by progressive organ dysfunction[1]. The clinical course and features of MPS I show considerable variety[1]. Historically, the broad clinical spectrum of MPS I has been categorized into three phenotypes: Hurler (early onset, rapid progression, cognitive impairment), Scheie (later onset, slower progression, preservation of cognition), and Hurler-Scheie (intermediate onset and progression, mild or absent cognitive impairment)[2, 3]. More recently, the preferred classification is two broader groups: severe (Hurler syndrome) and attenuated (Hurler-Scheie and Scheie syndrome)[4, 5].

The involvement of bone and joints in MPS I leads to disruption of the normal growth and joint development in affected patients[6, 7]. Disorders of bone and cartilage formation lead to abnormalities related to skeletal dysplasia (dysostosis multiplex) including gibbus deformity, scoliosis, degenerative joint disease, and marked short stature[5, 8]. Short stature is a consistent feature, with linear growth ceasing by the age of 3 years in the severe Hurler phenotype[8].

Enzyme replacement therapy (ERT) with aldurazyme® (laronidase, Biomarin Pharmaceutical Inc., Novato, CA, USA and Genzyme Corporation, Cambridge, MA, USA) has been available for MPS I patients since 2003 in the United States and the European Union, and since 2004 in Korea. The effectiveness of ERT has been observed in the form of significant and sustained reductions in urinary GAG excretion and liver and spleen volume [4, 9-12]. Improvements in pulmonary function and functional capacity have also been reported in several studies[4, 10, 11, 13].

To date, only a few studies have examined the effects of ERT on growth in patients with MPS I[9, 11, 12, 14, 15]. To our knowledge, no data are presently available for Asian MPS I patients. The objective of this retrospective study was to analyze the effect of ERT on growth patterns in 10 Korean MPS I patients with different phenotypes and to assess differences in growth at the time prior to ERT and after a minimum of 3 years of treatment with aldurazyme.

Materials and Methods

1. Patient population

Participants were recruited from the Department of Pediatrics, Samsung Medical Center. The Institute Review Board Committee at the Samsung Medical Center approved this study and patients, parents, or legal guardians provided informed consent. Data were obtained from clinical records

reviewed retrospectively.

All patients enrolled in this study were diagnosed with MPS I by biochemical determination of deficiency in IDUA enzyme activity in skin fibroblasts or peripheral blood leukocytes. In addition, molecular analysis of the IDUA gene was performed. This study included patients who had started ERT with aldurazyme between the ages of 2 and 15 years. Patients received weekly intravenous infusions of aldurazyme at 100 U/kg (0.58 mg/kg).

Height measurements were made with standard techniques using a stadiometer (accuracy to 1 mm). Initiation of treatment ±1 month was defined as "Start of ERT." Patients included in the analysis had more than one height measurement in the 24 month period before and after treatment. The final study population consisted of 10 patients; 6 males and 4 females.

Clinical phenotypes of Hurler, Hurler-Scheie and Scheie were divided into two groups - severe (Hurler) and attenuated (Hurler-Scheie and Scheie) - for evaluation of differences in growth patterns between different phenotypes. The type of mutation in the IDUA gene was based on amino acid changes and/or genomic sequences.

Two patients (P1, P2) in our study received recombinant human growth hormone (hGH) therapy. Their height data included in the analysis were restricted to measurements obtained during the period prior to initiation of hGH.

2. Statistical analysis

The raw height data of patients were plotted against normal height references for Korean boys and girls. Height data were standardized using published 2007 Korean growth charts and calculated values were presented as the standard deviation score (SDS). Z-scores stand for the number of standard deviations from the mean; a z-score of <-2 is generally indicative of short stature. Further calculations included mean changes in the patients' heights and z-scores (±SD) from baseline and annual growth velocity from the year before ERT to 3 years after ERT.

Standardized height data (z-scores) from 24 months before and after the start of ERT were analyzed using a piecewise regression and a mixed model. The patients were individually analyzed to assess the impact of clinical phenotype (severe versus attenuated) on growth.

Results

1. Patients

All 10 patients were born at term and were diagnosed as having MPS I at the median age of 4.4 years. All patients presented with typical clinical characteristics of MPS I, such as corneal clouding, joint stiffness, and coarse facial features. Of the 10 patients, 6 were male and 4 were female. Three patients were classified as Hurler, 6 as Hurler-Scheie, and 1 as Scheie.

The patients started ERT between the ages of 2 years 3 months and 14 years 10 months (median age of starting ERT was 7.7 years). Table 1 lists the demographic information, molecular characteristics, and clinical phenotypes of the patients.

2. Effect of ERT on Growth in patients with MPS I

For the whole sample (n=10; age range at start of ERT, 2 years 3 months-14 years 10 months),

the height at initiation of ERT ranged from 85 to 142.6 cm (median, 100.5 cm). The mean height SDS at the start of ERT was −2.82±3.36. The mean increase in height during 3 years of ERT was 16±5.6 cm. At the start of ERT, 3 boys and 3 girls had z−scores of < −2, indicative of short stature. The growth charts and the z−scores are shown in Figs. 1A, 1B, and 2. The arrows shown in Fig. 1 indicate the initiation of growth hormone therapy in two patients (P1, P2).

Annual changes in growth velocity were calculated in 8 out of a total of 10 patients. Two patients (P6, P10) who had started ERT before the age of 3 years (2 years 4 months and 2 years 3 months, respectively) were excluded due to different growth patterns in the growth spurt following birth; height data used in the analysis were restricted to the measurements obtained before initiation of hGH in one patient (P1) who received hGH therapy during the third year of ERT. The

Table 1. Demographic Information, Molecular Characteristics, and Clinical Phenotypes of 10 Korean Patients with MPS Type I

Patient	Sex	Age (year) at diagnosis	Age (year) at starting ERT	Current age (year)	Total laronidase exposure (weeks)	Phenotype	Type of mutation in IDUA	Exon	cDNA change	Amino acid change
P1	M	6.5	10.11	19.4	436	Hurler−Scheie	Missense	8	c.1037T>G	p.Leu346Arg
P2	M	4.1	7.9	16.11	476	Hurler−Scheie	Missense	8	c.1037T>G	p.Leu346Arg
P3	F	3.4	7.6	16.9	480	Hurler−Scheie	Insertion	6	c.704_705insC TGCT	p.Trp235Cysfs*84
							Missense	8	c.1037T>G	p.Leu346Arg
P4	M	10.9	14	22.5	436	Scheie	Missense	2	c.265C>T	p.Arg89Trp
							Nonsense	11	c.1601C>A	p.Ser534*
P5	M	4.8	3.11	11.8	400	Hurler−Scheie	NA	NA	NA	NA
P6	M	2.3	2.4	9.11	392	Hurler−Scheie	NA	NA	NA	NA
P7	M	6.10	11.10	20.2	432	Hurler−Scheie	Missense	8	c.1037T>G	p.Leu346Arg
P8	F	9.11	14.10	23.2	432	Hurler	Missense	8	c.1037T>G	p.Leu346Arg
P9	F	2.9	3	8.9	348	Hurler	Missense	2	c.236C>T	p.Ala79Val
							Missense	14	c.1882C>T	p.Arg628
P10	F	2.2	2.3	5.11	188	Hurler	Duplication	6	c.613_617dup	p.E207AfsX29
							Deletion	6	c.683delC	p.P228HfsX6

Abbreviations: P, patient; M, male; F, female; ERT, enzyme replacement therapy; IDUA, α−L−iduronidase; NA, notavailable.

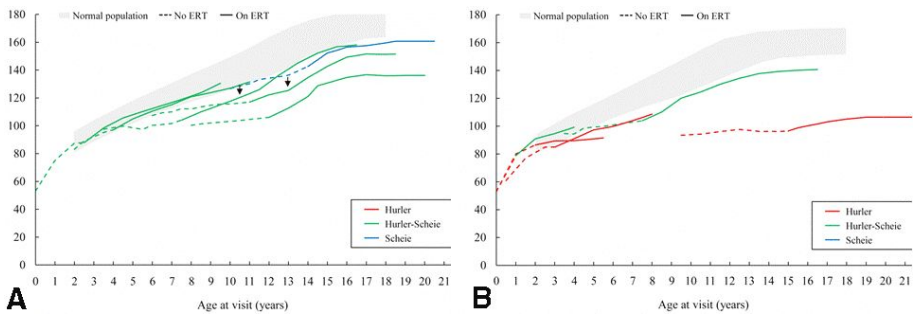

Fig. 1. Growth charts for MPS I patients. Growth before enzyme replacement therapy (ERT) is denoted as dotted lines; growth after ERT is shown as continuous lines. The shaded area indicates the height data (3rd to 97th percentile) of the normal population of children in Korea. The red lines represent patients with the Hurler phenotype, green lines are patients with Hurler−Scheie, and the blue lines show those with Scheie. The 2 arrows indicate the initiation of recombinant human growth hormone (hGH) in 2 patients. (A) Growth charts for boys with MPS I. (B) Growth charts for girls with MPS I.

increase in height was 3.3 cm (z-score=−0.21) the year before commencement of ERT, compared with 6.2 cm (z-score=0.17), 5.8 cm (z-score=0.07), and 3.8 cm (z-score=−0.4) in the first, second, and third years of the ERT, respectively (Figs. 3A and 3B).

1) Height z-score analysis

Overall analysis was performed with height z-scores of the 10 patients. The analysis showed that the slope of the regression after treatment was significantly different when compared with the slope before treatment (the estimated slopes before and after treatment were −0.037 and 0.004, respectively: difference in the slope, 0.04; P=0.022) (Fig. 4).

2) Impact of phenotype (severe versus attenuated) on growth

Before treatment, the estimated slope difference between the severe and attenuated groups was −0.072 (P=0.001), and it was −0.068 (P<0.0001) after treatment. No statistically significant differences were noted between groups when stratified according to phenotype (severe versus attenuated)

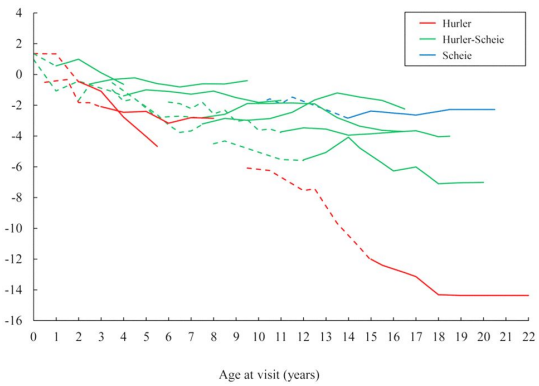

Fig. 2. Height z-scores in MPS I patients. Growth before enzyme replacement therapy (ERT) is denoted as dotted lines; growth after ERT is shown as continuous lines. The red lines represent patients with the Hurler phenotype, green lines are patients with Hurler-Scheie, and the blue lines indicate those with Scheie.

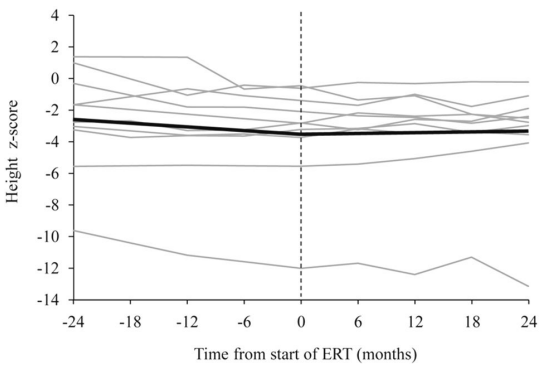

Fig. 4. Regression plot showing height z-scores before and after the start of enzyme replacement therapy (ERT). Gray lines indicate individual regression lines for each patient. The slope of regression was significantly increased after treatment compared with before treatment (difference in the slope, 0.04; P=0.022).

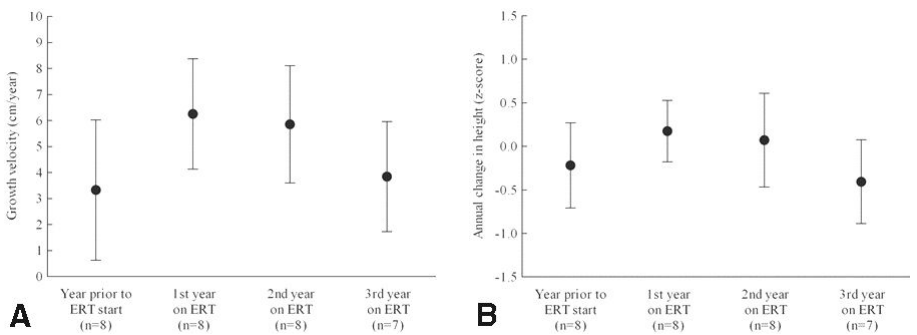

Fig. 3. Annual growth velocity and z-score changes in patients with MPS I who were more than 3 years old at the start of enzyme replacement therapy (ERT). (A) Annual growth velocity. (B) Z-score change.

(P=0.361). No significant difference was observed for height deficit at the start of treatment in terms of z-scores between the two groups (difference in z-score at the start of ERT, 1.97; P=0.641) (Fig. 5).

Discussion

This is the first study to report the impact of ERT on linear growth in Asian patients with MPS I. The data evaluated in this study represent the patient population from a single center and the same height measuring methods were applied to all patients; thus, the height changes recorded for the patients should be relatively accurate. All the patients are of the same ethnicity, so the data are unlikely to be confounded by ethnic differences.

When compared with the healthy population, MPS I patients show significantly different growth patterns. During the first 2 years of life, MPS I patients tend to grow faster than their age-matched normal peers[12]. After 2 years, MPS I patients grow significantly slower, with the difference between affected and healthy children increasing with age[8, 12]. Fig. 1A, 1B, and 2 reflect these characteristics in our patients. A longitudinal study with height data from pre and post-ERT allowed us to investigate the linear growth of children with MPS I. The patients' pre-ERT data could be interpreted as natural growth patterns in the absence of treatment. The individual growth curves of the raw height data and standardized height z-score data indicate that growth was retarded compared with the normal population as our patients grew older.

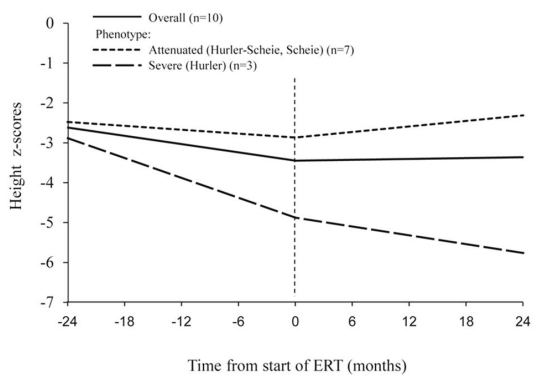

Fig. 5. Regression plot showing height z-scores before and after the start of enzyme replacement therapy (ERT) in groups stratified by phenotype (severe versus attenuated).

The impact of ERT with aldurazyme on growth in MPS I patients has been reported in a few studies. Wraith et al. noted that 7 patients who were younger than 5 years at initiation of ERT showed a net increase in height-for-age z-score after 52 weeks of treatment[12]. Kakkis et al. reported six prepubertal patients with an increase of 85 percent in height with a mean rate of increase from 2.80 cm per year to 5.17 cm per year at 52 weeks of ERT[9]. Sifuentes et al. reported a substantial increase in growth rate of 27% over baseline at the 1-year assessment in prepubertal patients and continuation of growth during the pubertal years[11]. The data from these studies show an increase in growth velocity after ERT that seems consistent with the results of our analysis.

In our study, height z-score analysis showed an overall increase in growth rate in the 2 year period after starting ERT, when compared with the 2 year period prior to treatment. (Fig. 4) Improvements in annual growth velocity and z-score change were evident, although some slowing down occurred in the 2nd and 3rd year compared with the 1st year on ERT. (Fig. 3) Two patients in our analysis (P4, P8) commenced ERT after pubertal age (14 years and 14 years 10 months, respectively). P4, who was diagnosed with Scheie syndrome, had a height SDS of -2.83 at the start of

ERT which was improved to −2.64 after 3 years of ERT. Height and z-scores gradually increased after ERT, even though the patient had started ERT at an older age. (Fig. 1B, 2) P8 was diagnosed with Hurler syndrome. She developed heart failure with moderate mitral and aortic valve regurgitation and was started on an angiotensin converting enzyme inhibitor. No significant progression of heart failure has occurred while the patient has been receiving ERT. The patient's height has been stationary during the years of ERT; the underlying cardiac complication may possibly have had an influence on the growth pattern of this patient. (Fig. 1B, 2) The 8 patients who started ERT in the prepubertal age had a mean SDS of −2.48±1.71 at the start of ERT, and a mean SDS of −2.37±1.27 2 years after ERT. The patients showed an overall improvement in growth after ERT, although phenotypic differences were seen. (Fig. 1A, 1B, 2)

In this study, 3 patients were classified as severe (Hurler) and 7 patients were classified as attenuated (Hurler-Scheie or Scheie). As shown in Fig. 5, the effect of ERT on linear growth was not favorable for the 3 patients with the severe phenotype. Statistical analysis did not indicate a significant difference when comparing the z-scores at the start of ERT between the 2 groups; however, the small sample sizes probably contributed to this lack of statistical significance and acted as a confounding factor. Estimated slopes of regression for pre and post treatment of both groups showed significant differences, with height deficit in the severe group more pronounced both before and after treatment, when compared with the attenuated group. The impact of ERT on growth in patients with the severe phenotype is likely to be diminished due to their more severe skeletal dysplasia with earlier bone and joint deformities and the further progression of their multiorgan dysfunction when compared with the patients with the attenuated phenotype[5].

Two brothers (P1, P2) were treated with recombinant hGH. Peak GH determined by the L-dopa-clonidine stimulation testing was normal, at 10.17 μg/L for P1 and 13.76 μg/L for P2, but hGH treatment was started due to stress associated with short stature and parental desire for treatment. P1 started ERT at the age of 10 years 11 months and received hGH treatment between the ages of 12 years 11 months and 17 years 4 months, at a dose of 0.033 mg/kg/day. Height SDS at the start of ERT was −3.73; at the time of initiation of hGH treatment after 2 years of ERT was −3.55, and was −4.05 at the time of cessation after 4 years and 5 months of hGH treatment. P2 had started ERT when he was 7 years 9 months old. His hGH treatment was initiated at the age of 10 years 7 months, at 0.033 mg/kg/day, and he is still receiving treatment at 16 years and 9 months of age. Height SDS at the time of ERT was −3.22; height SDS prior to hGH treatment after 3 years of ERT was −2.87; and his current height SDS after 6 years 2 months of hGH treatment at the age of 16 years and 9 months is −2.24. P2 was not diagnosed as GHD, but the hGH therapy seems to have had a moderate influence on growth velocity based on raw height data and changes in height SDS when compared with those of P1 as shown in Fig. 1A and 2. The fact that P2, who is the younger brother, started both ERT and hGH at a younger age than P1 should be taken into consideration.

Histologic examinations of a bone and cartilage biopsy in a patient with Hurler syndrome and a feline MPS I model have revealed disruption of

growth plate structure and defects in the orientation of chondrocytes, which are probably associated with GAG accumulation[16, 17]. This defect may in part interrupt proper skeletal formation, which in turn can contribute to the typical skeletal dysplasia of MPS I and cause inhibition of growth. ERT with aldurazyme is assumed to have little to no effect on the skeletal problems related to MPS I.[7, 18]. Several clinical studies have demonstrated improvements in joint mobility, respiratory function, and physical capacity after aldurazyme treatment[4, 10, 11, 13]. Overall improvements such as these probably had a positive effect on the improved growth rates observed in this current study. Three of 10 patients in our study received physiotherapy, which can be useful in ameliorating joint contractures and can result in an obvious increase in height.

A limitation of this study was its small number of patients analyzed – a consequence of the rarity of this disease. The small study number comprised phenotypes ranging from severe to attenuated, thereby giving a broad spectrum of individual data. The mean increases in the measured parameters also did not differ significantly between male and female patients during the first 3 years of life, and because our sample size was small, we did not perform any analyses by gender. Natural growth patterns for MPS I patients which are also important in evaluating the effect of ERT on growth, are difficult to obtain due to the rare incidence of the disease and ethical factors related with treatment initiation after diagnosis of MPS I.

In conclusion, the present data show an overall increase in growth after the initiation of ERT with aldurazyme. This indicates a positive impact of ERT on growth in patients with MPS I who without ERT would otherwise have shown more marked growth retardation. This is the first published report of the effect of ERT on growth in Asian patients with MPS I. Further long-term analyses in larger groups of patients will be needed for a more accurate evaluation.

Acknowledgments

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한 글 요 약

목적: I형 뮤코다당증 (MPS I)은 α-L-iduronidase 효소의 결핍으로 인하여 발생하는 리소좀 축적 질환으로, 광범위한 양상으로 다기관에 영향을 미친다. 저신장과 성장 속도의 감소는 MPS I의 중요한 특징이다. 본 연구에서는 효소 보충 요법이 MPS I 환자들의 성장에 미치는 효과에 대해 알아보기 위하여 단일 기관의 환자들을 대상으로 분석하였다.

방법: 2세에서 15세 사이에 효소 보충 요법을 시작하여 최소 3년 이상의 치료를 시행 받은 10명의 한국 MPS I 환자들의 키 측정치를 후향적으로 분석하였다. 효소 보충 요법 시작시의 평균 나이는 7년 7개월 이였으며, 남아는 6명, 여아는 4명 이였다. 키는 표준 편차(SDS)로 표현되었다. 효소 보충 요법 전과 후의 연간 성장 속도를 계산하였으며, 구분회귀모델을 이용하여 치료 전과 후의 키 z-score를 분석하였다. 표현형[(중증(Hurler) versus 경증(Hurler-Scheie, Scheie)]이 성장에 미치는 영향에 대해서는 개별 분석을 시행하였다.

결과: 효소 보충 요법 전 1년 동안의 연간 성장은 3.3 cm (z-score=-0.21) 였으며, 효소 보충 요법 후 1년, 2년, 3년에서는 각각 6.2 cm (z-score=0.17), 5.8 cm (z-score=0.07), 3.8 cm (z-score=-0.4) 이였다. 회귀분석 결과, 효소 보충 요법 전에 비하여 치료 후 기울기에 유의한 호전을 보였다(기울기 차이 =0.04; P=0.022). 중증과 경증 표현형 간의 치료 전

(P=0.001)과 후(P<0.0001)의 기울기 차이는 통계적으로 유의하였으나, 표현형에 따라 분석하였을 때 통계적으로 유의한 차이는 보이지 않았다.

결론: MPS I 환자들의 키 성장에 있어 aldurazyme 효소 보충 요법이 긍정적인 효과를 미치는 것으로 보인다.

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