Evaluate the Clinical and Laboratory Manifestations of Children With Type 6 of Mucopolysaccharidosis Before and After Enzyme Therapy: A Quasi-Experimental One Group Study

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Received: 03 Apr. 2023; Accepted: 21 Dec. 2023

Abstract- The purpose of this study is to evaluate the clinical and laboratory manifestations of children with mucopolysaccharidosis type 6 before and after enzyme therapy. In this quasi-experimental study, 8 patients with MPS-6 referred to the pediatric endocrinology department of Imam Reza Hospital in Mashhad were followed up for 12 months. The level of urinary glycosaminoglycan was measured to check the response to the treatment. The range of motion of the shoulder and elbow joints was evaluated using a goniometer, and abdominal ultrasound was performed to check the size of the liver and spleen in the midclavicular line. The 6-minute walking test and the 3-minute stair climbing test were performed for the patients at the mentioned times. The height and weight of the patients were also measured, and echocardiography was performed. Then patients underwent weekly enzyme treatment. One of the patients (seventh patient) was excluded from the study. Patients were treated with enzyme from the beginning of the study. The patients were evaluated at 12 months later. Statistical analysis showed that changes in urinary GAG level, height, weight, changes in 6-minute walk and range of motion (extension and flexion) of the shoulder were significant (P<0.05). Changes in liver and spleen size compared to height, climbing stairs, corneal opacity and heart changes after 12 months of enzyme therapy were not significant. It is suggested that even though this method of treatment is not definitive, that can be continued to improve the current condition of the patient.

Acta Med Iran 2024;62(Janyary-February):15-21.

Keywords: Clinical manifestations; Laboratory manifestations; Children; Type 6 of mucopolysaccharidosis; Enzyme therapy

Introduction

Mucopolysaccharidoses are a group of genetic diseases that, except for type II, are transmitted with an autosomal recessive inheritance pattern (1-3). Mucopolysaccharidoses are hereditary diseases that cause systemic and ocular symptoms due to lysosomal enzyme defects, these enzymes cause the conversion of glycosaminoglycans into subsequent metabolites, so defects in these enzymes cause the accumulation of these substances in the lysosomes of various tissues and tissues. It causes functional and structural disorders in these

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tissues. Different types of mucopolysaccharidoses have different manifestations depending on the enzyme defects and accumulation of different glycosaminoglycans (4-6). This syndrome can cause manifestations such as head and neck involvement, limb and spine deformities, hepatosplenomegaly, cardiac disorders, eye and ear disorders, brain damage and hydrocephalus. Sufferers often have no symptoms in early life (depending on the severity of the disease) and the symptoms appear after 2 or 3 years of age and progress depending on the severity of the disease and in severe cases lead to the death of the patient (6,7).

This disease is classified as one of the lysosomal storage diseases in which the lysosomal deficiency of the alpha-al-iduronidase enzyme leads to the accumulation of glycosaminoglycans in the cells and tissues of the body, especially the brain, bones, cartilage, eyes, respiratory tracts and heart valves (8).

Accumulation of these substances, including dermatan sulfate, keratan sulfate, and heparan sulfate, which are the main components of connective tissue, causes destruction and progressive damage to tissues and the appearance of disease symptoms. Skull and mouth are larger than usual, wide tongue, chin bone. Prominent, abnormal nose, rough face are the symptoms of the disease (8-10).

Sufferers do not show the disease during infancy or at birth and usually show the disease at the age of two years and later with walking problems. Gradually, other symptoms of this disease such as breathing problems, sleep problems, heart valve diseases, hearing disorders and corneal disorders also appear with age. Intelligence in these people is somewhat lower than healthy people (9-11).

There are different treatments for mucopolysaccharidosis. In the past, the limited treatment options for MPS VI led many physicians to adopt a palliative approach and focus on managing individual disease complications. For example, physical therapy to minimize contractures and joint stiffness and improve muscle strength, spinal fusion for spinal cord compression or progressive kyphosis, hernia repair, tonsillectomy, and adenoidectomy for airway obstruction or eustachian tube dysfunction (12). The bone marrow or hematopoietic stem cell replacement method is rarely used in the treatment of these patients due to the possibility of death and the phenomenon of transplant rejection and the difficulty of finding the best and most suitable compatible donors (13). Another effective treatment method is Enzyme Replacement Therapy (12,14). This is considered a safe and acceptable method (15). Considering that almost a decade has passed since enzyme replacement therapy for MPS-6 patients and bone marrow transplantation is not possible for all people, the researchers decided to conduct this study to evaluate the effects of this treatment in patients referred to Imam Reza Hospital in Mashhad. and considering that this disease involves many organs, several associated disorders were monitored in terms of enzyme treatment.

Materials and Methods

Study design and setting

The study was conducted as a quasi-experimental intervention of a single group before and after, and the sampling was non-probability and easy (During the years 2018 to 2019).

Study participants and sampling

In this study, 8 patients with MPS-6 referred to the pediatric endocrinology department of Imam Reza Hospital in Mashhad were followed up for 12 months. Patients were selected as convenience sampling.

Interventions

Patients were treated with enzyme from the beginning of the study. The method of treatment was that Naglazyme was injected at a dose of 100 U/K weekly. The injection was done as an intravenous infusion based on the child's weight with diluted normal saline at a rate of 2 CC/Kg per hour. The total volume was injected over 2-3 hours. After diluting the drug, it was injected immediately. Each vial was used for one session and was removed from the refrigerator 20 minutes before use to reach room temperature

Data collection tool and technique

The level of urinary glycosaminoglycan was measured to check the response to the treatment. Also, the range of motion of the shoulder and elbow joints was evaluated using a goniometer, and abdominal ultrasound was performed to check the size of the liver and spleen in the midclavicular line. The 6-minute walking test and the 3-minute stair climbing test were performed for the patients at the mentioned times. At these times, the height and weight of the patients were also measured, and echocardiography was performed to examine the heart of the patients.

In this study, patients underwent weekly enzyme treatment. One of the patients (seventh patient) was excluded from the study due to non-referral for necessary follow-up, and the data of 7 patients were finally

evaluated and analyzed. Patients were treated with enzyme from the beginning of the study. The method of treatment was that Nagla zyme was injected at a dose of 100 U/K weekly. The injection was done as an intravenous infusion based on the child's weight with diluted normal saline at a rate of 2 CC/Kg per hour. The total volume was injected over 2-3 hours. After diluting the drug, it was injected immediately. Each vial was used for one session and was removed from the refrigerator 20 minutes before use to reach room temperature. Necessary explanations were given to the parents and after receiving the informed consent, the patients were included in the study. Then the patients were evaluated at the beginning of the treatment and 12 months later.

Data analysis

Finally, the obtained data were analyzed with SPSS21 statistical software. Descriptive statistics were used to describe the data, and Smirnov's Kolmogorov test was used to check normality, and all quantitative data had a normal distribution. Paired t-test was used to compare changes in quantitative data, and Wilcoxon test was used to check changes in cardiac disorders. McNamar's test was used to check corneal opacity. A significance level of 0.05 was considered.

Results

The average age of patients at the start of treatment was 47.28±17.25 months. Out of 7 patients, one (14.28%) was female and the rest (85.72%) were male. The average age of disease diagnosis was 35.57±15.75 months with a maximum and a mean of 19-63 months. The statistical results of paired t test regarding changes in urinary GAG levels of patients during the follow-up period were significant (*P*=0.008). Also, the Paired t test was significant regarding the trend of height changes of patients during the follow-up period, i.e. at the beginning of treatment and one year after treatment (*P*=0.001). Also, the changes in patients' weight (*P*=0.001) and Z score (*P*=0.014) had a statistically significant difference during the follow-up period (table 1).

Table 1. Comparison of urinary GAG levels, height, weight of patients before and after treatment

Variable	Before Mean±std	After Mean±std	Paired t test
Urinary GAG levels	31.97±13.82	13.74±5.19	*P*= 0.008
Height	91.57±6.02	96.57±5.25	*P*=0.001
Weight	13.78±2.09	15.78±2.23	*P*=0.001

The paired t test showed that the changes in liver size compared to height during the follow-up period were not significant (*P*=0.129). Spleen size was also examined in relation to patients' height during the follow-up and the results showed that changes in spleen size compared to patients' height for one year were different. It was not statistically significant (*P*=0.609) (table 2).

Table 2. Comparison of liver and spleen size compared to height of patients before and after treatment

Variable	Before Mean±std	After Mean±std	Paired t test
Liver size compared to height	1.14±.17	1.07±.17	*P*=0.129
Spleen size compared to height	.84±.09	.86±.15	*P*=0.609

Also, changes in spleen size were not significant regardless of height after 12 months of follow-up (*P*=0.178). Also, the changes in liver size were not significant regardless of height (*P*=0.779) (Table 3).

The results of the paired t test indicated the significance of the changes in the 6-minute walk test during the follow-up period (*P*=0.02), so that children's walking had significantly improved after 12 months. But the results of statistical analysis showed that the changes observed after 12 months were not significant in the results of the test of climbing the stairs in 3 minutes (*P*=0.128). The maximum range of motion of shoulder extension was measured in degrees using a goniometer. The results of the paired t test were significant regarding

the changes in the range of motion of the right (*P*=0.002) and left (*P*=0.001) shoulders of the patients regarding extension and It showed that the mean and maximum range of motion of the right and left shoulder in extension had increased in all patients after 12 months. Also, the results of the paired t test regarding the changes in the range of motion of the right and left shoulders of the patients regarding flexion were significant (*P*=0.002) and It showed that the mean and maximum range of motion of the right and left shoulder in flexion had increased in all patients after 12 months. The results of the paired t test regarding the changes in the range of motion of the right and left elbows of the patients regarding extension were significant (*P*=0.001) and indicated that the minimum and maximum range of motion of the right and left elbows in extension in all patients after It had increased by 12 months (Table 4).

Examination of patients with echocardiography showed myxomatous & thick heart valves, but no significant stenosis was observed in any of the valves at the beginning of treatment and after 12 months, and only one patient had mild aortic valve insufficiency before and after treatment. There was no significant correlation between the findings before and after the treatment with the Wilcoxon test (*P*=0.99). Also, according to the Wilcoxon test, there was no significant relationship between mitral valve insufficiency (*P*=0.10), pulmonary valve insufficiency (*P*=0.15) and tricuspid valve insufficiency (*P*=0.65) at the beginning of treatment and after 12 months. In the general examination of valvular heart diseases, there was no significant relationship between the findings at the beginning of treatment and after 12 months with the Wilcoxon test (*P*=0.59) (Table 5).

Table 3. Comparison of liver and spleen size of patients before and after treatment

Variable	Before Mean±std	After Mean±std	Paired t test
Liver size	104.71±10.02	103.43±16.39	*P*=0/779
Spleen size	77.42±9.67	84.28±15.99	*P*=0.178

Table 4. Comparison of motor activities before and after treatment

Variable	Before Mean±std	After Mean±std	Paired t test
6-minute walking test	221.14 ± 79.08	333.71 ± 102.93	*P*=0.02
Climbing the stairs in 3 minutes	93.57 ± 59.48	123 ± 83.07	*P*=0.128
Maximum range of motion of the right shoulder in extension	30 ± 10.80	51.42 ± 8.01	*P*=0.002
Maximum range of motion of the left shoulder in extension	29.28 ± 10.57	50.71 ± 7.31	*P*=0.001
Maximum range of motion of the right shoulder in flection	60.0 ± 13.54	86.42 ± 5.56	*P*=0.002
Maximum range of motion of the left shoulder in flection	60.0 ± 13.54	86.42 ± 5.56	*P*=0.002
Maximum range of motion of the right elbow in extension	132.14 ± 20.59	158.57 ± 19.51	*P*=0.001
Maximum range of motion of the left elbow in extension	132.14 ± 20.59	158.57 ± 19.51	*P*=0.001

Table 5. Comparison of condition of heart valves before and after treatment

Valve failure status	Number	Percent	Wilcoxon test(z)
No failure	1	14.3	*P*=0.59
Mitral failure	2	28.6	
Multiple failure	4	57.1	

Discussion

Examining the urinary GAG level of patients showed that the changes of this variable after 12 months of treatment were significant, so that the average urinary GAG level was significantly reduced after 12 months. The findings of the present study showed the appropriate effectiveness of Gal Sulfase treatment on the results of walking test in six minutes, the maximum range of motion of the shoulder and elbow, and the level of urinary GAG, but it did not have a significant effect on the other investigated cases. Urinary GAG represents the amount of GAG that is secreted by the kidneys. In mucopolysaccharidosis type 6 patients, GAG accumulation in different organs causes many problems. Urinary GAG level indicates and reflects the amount of GAG accumulation in different tissues. By reducing the urinary GAG level, the amount of accumulation of this substance in different organs also decreases. The findings of the present study showed a clear decrease in urinary GAG during treatment. This finding is consistent with the study by Hsiang-Yu Lin et al and the study by Brunelli Mj *et al*., They also reported a significant decrease in urinary GAG levels after treatment with Gal sulfase (16).

In this study, the changes in the height and weight of the patients were investigated and the results showed that the height and weight of the patients increased during the treatment and had a statistically significant difference compared to the beginning of the treatment, so that the average height and weight after 12 months of treatment was significantly higher than the average at the beginning of treatment. Also, in the examination of individual patients in terms of height and weight, it showed an increasing trend. Examining the z score of the patients also showed that the z score had improved in most of the patients after the treatment. This finding is not consistent with the study of Brunelli *et al*., In their study, no significant and clear difference was observed between Gal Sulfase and placebo in terms of the effect on height and weight changes (16).

In the present study, to remove the confounding variable of age and its effect on the size of the liver and spleen, these sizes were examined as the length of the liver and spleen in relation to the height of the patients. The results showed that the changes in liver and spleen size during the treatment were not significant. In such a way that the average size of liver and spleen after 12 months was not significantly different from the beginning of treatment. In the examination of individual patients, the size of the liver decreased in 4 patients and increased in one patient, and in two patients, it did not change after 12 months compared to the start of treatment. Also, the size of the spleen decreased in two patients, did not change in one patient, and increased in 4 patients. This finding is consistent with the study by Hsiang-Yu Lin *et al*., and the study by Brunelli Mj *et al*., They also confirmed this finding (16,17).

Another finding in this study was related to the results of the patients' six-minute walk test. The results of the statistical test showed that the average result of the six-minute walk test after 12 months of treatment was significantly higher than the average at the beginning of the treatment. Also, the investigation on individual patients showed an increasing trend. Considering that the age of the patients at the beginning of the study was at the level where they were able to walk, the age variable does not seem to be effective in improving the results of this test after treatment. This finding showed the good effect of Gal Sulfase drug in improving muscle, bone strength and movement ability of patients. In the study of Hsiang-Yu Lin *et al*., on 9 Taiwanese patients, it showed that 6 patients improved in the 6-minute walking test with an average of 150 meters (17). In the study of Brunelli Mj *et al*., after 24 weeks of treatment, an improvement in the 12-minute walking test with an average of 92 meters was observed (16).

In examining the 3-minute stair climbing test, the statistical test about the changes in the test result after 12 months of treatment was not significant. So that the average result of the stair climbing test within 3 minutes after the treatment was not significantly different from the beginning of the treatment. Also, the examination of each patient showed that 5 patients climbed more stairs after treatment, and one patient did not change, and one patient climbed fewer stairs, which was probably due to the aggravation of vision problems. In the study of Hsiang-Yu Lin *et al*., three patients showed an increase in the stair climbing test in 3 minutes with an average of 60 steps (17), but in the study of Brunelli Mj *et al*., no statistically significant difference was observed (16).

Also, in the examination of the maximum range of motion of the elbow and shoulder joints in the present study, it was found that the trend of changes in the maximum range of motion of the right and left shoulder in terms of degrees in extension and flexion increased significantly after 12 months of treatment and there was a significant increase in the maximum range of motion of the right and left elbows in extension. These findings show the good effect of Gal Sulfase treatment on the maximum range of motion of shoulder and elbow joints.

Considering that these two joints play an important role in daily functions and performing activities, enzyme replacement therapy can increase the quality of life of patients. In Hsiang-Yu Lin's study, shoulder range of motion improved in all 9 patients and joint pain and stiffness decreased (17). Also, this finding is consistent with the study of Harmtaz *et al*., and the study of Horovitz *et al*., (18,5).

In the examination of corneal opacity in the studied patients, 4 patients had corneal opacity at the beginning of the study, while 5 patients had bilateral diffuse corneal opacity after 12 months of treatment but statistically, there was no significant difference between the findings before and after the treatment. In their study of 7 patients, Pitz *et al.*, showed that all 7 patients suffered from corneal stromal opacities However, during treatment with enzyme replacement and a follow-up period of three and a half years, visual function and eye findings did not worsen in six out of seven MPS VI patients (19).

In the cardiac examination performed with echocardiography, none of the patients had valvular stenosis before or after treatment. One patient had mild aortic valve insufficiency, and one patient had mild pulmonary valve insufficiency that did not change. But two patients who had no problem at the beginning of the treatment, found mild pulmonary insufficiency after 12 months. In mitral valve examination, two patients were healthy at the beginning of treatment and after 12 months they found mild regurgitation, and one patient's degree of mitral regurgitation changed from mild to moderate. There was no change in three patients who had degrees of mitral regurgitation, but mild mitral regurgitation was resolved in one patient after 12 months of treatment.

In tricuspid examination, two patients had mild regurgitation before and after treatment, which did not change. The severity of regurgitation increased from minor to mild in one patient, and one patient who was healthy at the start of treatment developed moderate valvular regurgitation after 12 months. The severity of regurgitation decreased from moderate to mild in one patient and two patients did not have valvular disorder before and after 12 months. In the examination done after treatment, one patient had mild cardiomyopathy, and in one patient, mild atrium and left ventricular dilatation was seen, the left ventricular function was borderline, but the other patients' left ventricular function was normal.

In none of the mentioned cases, as well as in the general examination of heart diseases, there was no statistically significant difference between the findings at the beginning of treatment and 12 months after treatment, and enzyme replacement therapy had no significant effects on heart valvular manifestations. This finding is consistent with the study by Harmatz et al. and Giugliani *et al*., In their study, pulmonary function remained unchanged for both groups and no significant effect on heart function was observed (20,21).

Limitations

One of the limitations of the present study is the small number of studied samples. Geographical dispersion and problems in referring for necessary follow-ups were also among other limitations, and for this reason, one patient was excluded from the study. It seems necessary to conduct this study on a larger scale and with a larger sample size.

According to the findings of the present study, enzyme therapy improves the physical symptoms of the disease and has a positive effect on the child's weight, height and movement activity. But even though it affects the size of the liver, spleen and cardiac changes, these changes were not statistically significant. Therefore, it is suggested that even though this method of treatment is not definitive, it should be continued to improve the current condition of the patient.

Acknowledgments

One of the strong points of the present study was the cooperation of experienced and skilled pediatric endocrinology professors at Mashhad University of Medical Sciences in such a way that all diagnosed patients were introduced to participate in the study. We are grateful to all respected specialists, patients and their families, also from Mashhad University of Medical Sciences, who supported the project financially.

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