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Economic Evaluation

Healthcare Resource Utilization and the Cost of Care for Mucopolysaccharidosis I Patients in Iran

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ABSTRACT

Background: Mucopolysaccharidosis I (MPS-I) is one of the most common types of MPS and lysosomal storage diseases, which impose considerable amount of economic burden on society. **Objectives:** The aim of this study was to examine the cost drivers in the treatment of MPS-I patients in Iran. **Methods:** This is a cost-analysis study. The prevalence approach was used to evaluate costs from the healthcare payer's perspective. The number of patients found to have α -L-iduronidase deficiency was identified using the national registry database of the Ministry of Health (MOH). The direct medical costs of the patients were evaluated. Prescriptions; medical interventions; inpatient, outpatient, and diagnostic services, and also their costs were extracted from the patient's profiles in Iran Food and Drug Administration (IFDA). The prices of the medical services were taken out from Iranian medical tariff book 2014-15. Data extraction was performed from January

2017 to March 2018. **Results:** Sixty-six patients were registered as MPS-I in MOH databases. The average annual healthcare cost for every patient was \$87971.99, 96.9% of which was allocated to medication therapy. Therapeutic and diagnostic services costs (2.4% and 0.7% correspondingly) were ranked second and third, respectively, but with huge differences in medication cost. **Conclusions:** The average annual cost of treatment for MPS-I patients is as high as 16.2 times the GDP per capita in Iran. The highest share of the cost belongs to medication. Selecting appropriate strategies for reducing the birth of a child with MPS could support allocative efficiency of the limited resources effectively. **Keywords:** healthcare, Iran, laronidase, MPS-I, resource utilization.

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Introduction

Lysosomal storage disorders are a group of inherited metabolic disorders, and about 45 types of them are known. Mucopolysaccharidosis I (MPS-I) is one of the MPS types and is a lysosomal storage disease that is inherited in an autosomal recessive pattern. This disease is due to deficiency in α -L-iduronidase, which leads to accumulation of the glycosaminoglycans dermatan sulfate and heparan sulfate in the cells.¹ The prevalence of MPS-I is approximately 1/100 000 births.^{2–5}

MPS-I has been subdivided syndromically into 3: Hurler syndrome, Hurler-Scheie syndrome, and Scheie syndrome.³ The symptoms in infants with Hurler syndrome, which also is known as severe MPS-I, are umbilical or inguinal hernia, frequent upper-respiratory-tract infections, coarsening of the facial

features, decreasing growth, hearing loss, and progressive skeletal dysplasia (dysostosis multiplex).^{6–10}

Attenuated MPS-I (Hurler-Scheie syndrome and Scheie syndrome) usually starts at the age of 3-10 years, and the severity and course of the disease are variable. The most common symptoms in this subdivision of the disease include hepatomegaly, dysostosis multiplex, corneal clouding, and sleep disturbance or snoring.¹¹

Although no definitive cure has been found for MPS-I, some treatments are available, including those that address the clinical phenotype (such as surgery to correct hernias) or the mutant protein (hematopoietic stem-cell transplantation and enzyme replacement therapy [ERT] with laronidase). Laronidase, or recombinant α -L-iduronidase (Aldurazyme[®]), is manufactured by Biomarin Pharmaceutical Inc. and Genzyme Corporation, USA.

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Table 1 – Laronidase (Aldurazyme) and their related cost by age group (USD).

| Age (year) | Number of laronidase (Aldurazyme) vials consumed annually (95% CI) | Annual cost USD (95% CI) |
|--------------------------------------|--|--------------------------|
| 1-3 | 76 ± 41 | 40235 ± 21705 |
| 3.1-6 | 119 ± 26 | 63000 ± 13764 |
| 6.1-9 | 163 ± 21 | 86294 ± 11117 |
| 9.1-12 | 206 ± 32 | 109058 ± 16941 |
| 12.1-15 | 250 ± 52 | 132353 ± 27529 |
| >15 | 285 ± 70 | 150882 ± 37059 |
| Total annual mean (age in dependent) | 161 ± 22 | 85235.29 ± 11647 |

CI indicates confidence interval.

The dosage of laronidase is 0.58 mg/kg body weight, administered once weekly as an intravenous (IV) infusion.^{12–19}

Although MPS-I is a rare lysosomal storage disease, the cost of care is disproportionally high. Economic burden and the costs of MPS disease have rarely been studied in Iran and other developing countries. The aim of this study was to examine the cost drivers in the management of MPS-I patients in Iran.

Methods

The prevalence approach was used to evaluate the costs of the management of MPS-I patients from the healthcare payer perspective. The prevalence of disease was calculated with regard to all available cases during a given year.

Both demographic and health resource utilization variables were addressed in this study.

Data Source

The national registry database of Ministry of Health (MOH) was used to identify individuals with α -L-iduronidase enzyme deficiency and their healthcare use. This electronic registry of MPS-I patients was started from January 3, 2015, in Iran.

Likewise, patient's profiles in Iran Food and Drug Administration (IFDA) were used to extract the medications prescribed for MPS-I patients.²⁰

The prices were converted from rials to USD based on the official exchange rate declared by the Central Bank of Iran in 2017 (\$1.00 = 34117 Iranian rials).²¹ Data extraction was performed from January 2017 to March 2018. The extracted data were analyzed descriptively.

Types of the Costs

To investigate the distribution of the cost drivers, health services were divided into 3 categories: medication, diagnostic, and therapeutic services. The medication cost was calculated on the basis of patient age groups. The patients were classified into 6 groups: 1-3, 3.1-6, 6.1-9, 9.1-12, 12.1-15, and above 15 years old. Medication cost was estimated by multiplying annual number of laronidase vials consumed in each age group to the price of laronidase (Table 1).

Diagnostic services included laboratory tests, imaging, and cardiopulmonary services, and therapeutic services included physician visits, surgery, and supportive services. Nevertheless, because the frequency of use of these services was not recorded in patient profiles, these frequencies were collected through

interviews with clinicians. Because these services are normally age independent, we did not use age subgroups for analysis of these costs. Iranian medical tariff book was used to calculate the cost of diagnostic and therapeutic services. Total cost of diagnostic and therapeutic services was calculated by multiplying the frequency and the price of each service. The summary of the results is presented in Tables 2 and 3.

Statistical Analysis

All analyses were performed with SPSS 16.0 software. The significance of the Shapiro test ($P < .001$) indicated a non-normal distribution of samples. The χ^2 test of independence was done to examine the relation between cost and sex.

Results

The review of IFDA database showed that 66 patients with MPS-I had been registered by October 24, 2017 (29 women and 37 men). The mean patient age was 6 years. The youngest and oldest patients were 1 and 17 years of age, respectively. The characteristics of the MPS-I patients are summarized in Table 4.

Laronidase, the only medicine for MPS-I in Iran, is ordered, financed, and distributed by IFDA as an MOH organization. The MOH also provides a service package including a vast range of laboratory, diagnostic, and in- and outpatient services for MPS-I patients. Nearly all expenditures of MPS-I treatment are covered by the national healthcare system.

Examining the process of patient registration in Iran showed that no valid and reliable diagnostic test is used to identify the types of MPS-I. Thus, all patients are registered under one category.

The MOH manages services through the clinics located across various cities in Iran. Patients are referred to these clinics and receive their medication and other healthcare services based on physician's decisions. It is important to note that currently there is no evidenced-based treatment protocol for managing these patients in Iran.

Our results showed that the most used resources were the medications with the annual cost of \$85235.29 per patient. Therapeutic services took up an annual cost of \$2149.29 followed by diagnostic services at \$587.41 per patient per year. The percentage share of each cost group is illustrated in Figure 1.

The χ^2 test of independence was performed to examine the relationship between cost and sex. The relationship between these variables was not significant ($X^2[9, N = 66] = 12.37; P = .19$).

The cost drivers within each cost group are displayed in Tables 1 to 3 (based on healthcare service package).

As Figure 1 shows, the main component of direct cost came from the medication cost (96.9%). Therapeutic and diagnostic costs were ranked second and third, respectively, but with huge differences. The amount of these costs clearly illustrates that the cost of care for MPS-I patients is very high and unaffordable for many of the patients' families, along with the additional challenge it poses for government funding.

Discussion

Our data showed that the average annual cost of treatment for each MPS-I patient (\$87971.99) is 16.2 times higher than the GDP per capita in Iran.²² This is particularly important when comparing this ratio to other high-cost diseases, such as hemophilia, breast cancer, and type 2 diabetes, with annual cost per capita of \$15130 (2.8 GDP per capita in 2016), \$7304.15 (1.4 GDP per capita in 2013), and \$824.60 (0.16 GDP per capita in 2011), respectively.^{23–25}

Table 2 – Type and frequency of therapeutic services and their annual costs.

| Category | Item | Frequency | Annual cost per capita (USD) | Percentage of total cost per capita |
|--------------------|--------------------------------------|-------------------|------------------------------|-------------------------------------|
| Physician visits | Physical therapy | 30 | 531.82 | 0.6 |
| | Speech therapy | 30 | 474.84 | 0.54 |
| | Audio metry | 1 | 53.81 | 0.06 |
| | Endocrinology | 4 | 52.99 | 0.06 |
| | Cardiologist | 3 | 39.75 | 0.05 |
| | Orthopedic | 2 | 26.50 | 0.03 |
| | Neurologist | 2 | 26.50 | 0.03 |
| | ENT | 1 | 13.25 | 0.01 |
| | Ophthalmologist | 1 | 13.25 | 0.01 |
| | Physiatrist | 1 | 13.25 | 0.01 |
| | Gastroenterologist | 1 | 13.25 | 0.01 |
| | Hematologist | 1 | 13.25 | 0.01 |
| | Infectious disease specialist | 0.5* | 6.62 | 0.008 |
| | Psychiatrist | 0.5 | 6.62 | 0.008 |
| | Total | | | 1285.69 |
| Surgery | Orthopedic and spinal surgery | 0.05 [†] | 278.45 | 0.32 |
| | Hernia repair | 0.1 [‡] | 146.55 | 0.17 |
| | Ventriculoperitoneal shunt | 0.04 [§] | 58.62 | 0.07 |
| | Carpal tunnel repair | 0.05 | 51.29 | 0.06 |
| | Surgical valve repair or replacement | 0.02 [¶] | 35.17 | 0.04 |
| | Myringotomy (ear tubes) | 0.05 | 29.31 | 0.03 |
| | Adenoidectomy/tonsillectomy | 0.04 | 23.45 | 0.02 |
| | Total | | | 622.86 |
| Supportive service | Dentistry | 2 | 240.74 | 0.27 |
| Total | | | 2149.29 | 2.4 |

ENT indicates ear, nose and throat.

* The frequency use of this service is 1 in 2 years.

† The frequency use of this service is 1 in 20 years.

‡ The frequency use of this service is 1 in 10 years.

§ The frequency use of this service is 1 in 25 years.

¶ The frequency use of this service is 1 in 50 years.

The results showed noticeably that medication costs had the largest share of healthcare resources at \$85 235.29 (96.9%), followed by therapeutic services at \$2149.29 (2.4%). Therefore, it would be valuable to critically evaluate medication therapy of these patients to ensure the best clinical effectiveness and efficient use of financial recourses.

The review of patient's profiles demonstrated that although pharmaceutical companies are doing tests only for initial recognition of the patients for free, sophisticated and valid tests have not been performed in Iran to identify MPS-I subgroups, such as Hurler, Hurler-Scheie, and Scheie. Thus even though treatment protocols for different types of MPS-I vary significantly, all patients are registered in a single group and are treated equally in Iran. It is stated that Hurler form is characterized by the presence of neurological involvement.^{26,27} Likewise, many studies have shown that laronidase does not cross the blood–brain barrier and thus has no medical indication for this form of the disease.^{14,15,28} On the other hand, although laronidase, which is one of the most expensive medicines in Iran and perhaps in many other countries, is not effective for Hurler form,^{27–29} all Hurler patients are receiving laronidase without medical indication.

The age distribution of the patients could also support the above argument. Table 4 shows that 89.4% of the patients were under 10 years of age. This suggests that the severe and moderate forms of the disease (Hurler and Hurler-Scheie forms), which are characterized by degenerative manifestations and low life expectancy,^{10,30} are more common in Iran. This evidence could demonstrate that the current policies and strategies of IFDA for

managing MPS-I disease have caused considerable amounts of over use and misuse of medication and consequently waste of resources. Although laronidase is covered by IFDA mainly based on humanitarian and ethical principles, it is necessary to consider the outcome of the medication to ensure efficient use of resources. This clearly suggests that the IFDA should critically revise its policy and use an evidence-based clinical practice guideline to ensure the best clinical effectiveness and efficient use of financial recourses.

Different countries have different management policies for MPS-I patients. We found only 2 studies that reported cost of illness for MPS patients. One of them was performed among MPS patients in some European countries, and the other was performed in the UK.^{31,32} The result of Matta's study demonstrated that Germany has the highest annual cost per patient among European countries (\$24 5078.99). The annual cost per patient was similar in Italy and Spain (\$99 379.75 and \$110 456.41, respectively) and at a lower level in France and Hungary (\$30 415.45 and \$28 695.14, respectively).³¹ Nevertheless, in both adults and children, the 2 main components of the cost were medication and medical visits.

Comparison of our results with Matta's study showed that the cost components in EU are more than those in Iran. Although medication cost has the largest share of healthcare resources used in Iran and most European countries (Germany 58.09%, Spain 34.6%, Italy 56.39%, Hungry 0.06%, and France 0.01%),³¹ this component in Iran is significantly higher than that in EU countries (Iran 96.9%). This could be attributed to lack of social supportive cares for Iranian MPS-I patients.

Table 3 – Type and frequency of diagnostic services and their annual costs.

| Category | Item | Frequency | Annual cost per capita (USD) | Percentage of total cost per capita |
|-----------------|-----------------------------|-----------|------------------------------|-------------------------------------|
| Laboratory | GAG | 1 | 58.62 | 0.07 |
| | Serum immunoelectrophoresis | 1 | 28.27 | 0.03 |
| | Platelets | 1 | 0.69 | 0.0007 |
| | Hemoglobin | 1 | 0.46 | 0.0005 |
| | Antibody sample | 0 | | |
| | Mutation analysis | * | | |
| | L-iduronidase | * | | |
| | Other† | 1 | 39.28 | 0.04 |
| | Total | | 127.32 | 0.14 |
| Cardiopulmonary | Forced vital capacity | 4 | 113.96 | 0.13 |
| | Echocardiography | 1 | 60.15 | 0.07 |
| | Peak expiratory flow rate | 4 | 37.99 | 0.04 |
| | Electrocardiogram | 4 | 25.32 | 0.03 |
| | Total | | 237.42 | 0.27 |
| Imaging | Radiology/MRI/CT Scan | 1 | 222.67 | 0.25 |
| Total | | | 587.41 | 0.7 |

CT indicate computed tomography; MRI, magnetic resonance imaging; GAG, glycosaminoglycan.

* Enzymatic and genetic tests are done by the importing company for free.

† Iron, transferrin, ferritin, vitamin B12, prothrombin, thromboplastin time, aspartate amino transferase, alanine aminotransferase, alkaline phosphatase, calcium, phosphorus, albumin, total protein, and direct and total bilirubin.

Social supportive care for MPS patients and their families is very important and could positively affect their quality of life. The results of our study demonstrated that the cost of social care for MPS patients is very high in England and other European countries.^{31,32}

Comparison between the cost drivers of MPS patients in Iran and England showed that although medication costs are much close to each other, the average annual costs of MPS-I in the UK were almost 2 times higher than that in Iran.³² Nonetheless, it is important to note that comparing the net costs between the countries may cause misunderstanding and does not show the impact of the cost for each country. Therefore, to standardize the expenditures, it is better to express the costs based on GDP per capita of the countries. This comparison could provide a more appropriate and pragmatic vision for cost analysis. Thus, although the average annual cost of care for MPS-I patients in Germany, as the highest cost per patient among European countries, was 5.7 times higher than their GDP per capita in 2012,^{22,31} it was 16.2 times higher than GDP per capita in Iran in 2017. This could show clearly that although the net cost of care for MPS-I patients is

high in all countries, the meaning and value of the cost for Iran, and maybe for many middle- and low-income countries, is significantly greater than the high-income countries. This could in turn imply that the cost of care for MPS-I patients is not only unaffordable for patients' families, but also difficult for many governments. Thus it might be good to select strategies that could reduce the birth rate of children with MPS. This could include performing genetic tests before marriage and during the pregnancy of high-risk women.

Limitations

Our study has 3 limitations. First, because the frequency of use and the cost of diagnostic and therapeutic services were not recorded in patients' profiles, these data were obtained from interview with clinicians. As a result, our cost information may not be completely accurate. Nevertheless, as the costs of diagnostic and therapeutic services were only 3.1% of the total

Table 4 – The summarized characteristics of Mucopolysaccharidosis I patients.

| Characteristic | Number (%) |
|---------------------------------|------------|
| Total patient | 66 (100) |
| Median age (year) | 6 |
| Male | 37 (56) |
| Female | 29 (44) |
| Current age distribution (year) | |
| 1-3 | 16 (24.2) |
| 3.1-6 | 20 (30.3) |
| 6.1-9 | 20 (30.3) |
| 9.1-12 | 7 (10.6) |
| 12.1-15 | 1 (1.5) |
| >15 | 2 (3.1) |

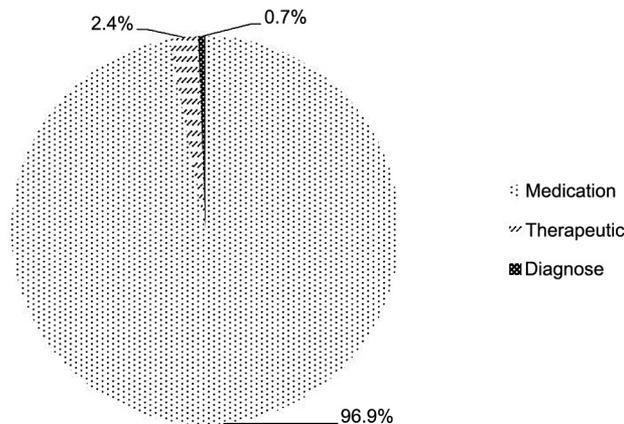


Fig. 1 – Percentage share of MPS-I cost drivers.

cost of care for MPS-I patients, we do not expect that this inaccuracy would affect our results significantly. Second, because not all information about the patients, such as weight and type of disease, was recorded accurately in patients' profiles, we could not perform a statistical analysis to reveal the association between characteristics of the patients and their healthcare costs. Finally, the absence of a single and comprehensive data source for all estimates was the third limitation of this study, which may decrease the accuracy of the results. Nonetheless, we tried to double-check patients' data with both IFDA and the clinic to minimize this inaccuracy as much as possible.

Conclusions

The average annual cost of treatment for MPS-I patients is as high as 16.2 times the GDP per capita in Iran. The highest share of the cost belongs to medication. Many lines of evidence demonstrated that the current policies and strategies of IFDA for managing MPS-I disease have caused considerable amount of over use and misuse of medication; therefore a local evidence-based clinical practice guideline could help IFDA to improve the efficient use of financial recourses.

Selecting appropriate strategies for reducing the birth rate of children with MPS could also support allocative efficiency of the limited resources effectively.

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