Management of Mucopolysaccharidosis Type I in Saudi Arabia: Insights from Saudi Arabia

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Abstract
Mucopolysaccharidosis (MPS) is a group of rare disorders that are characterized by intracellular accumulation of glycosaminoglycans with subsequent cellular and organ dysfunction. In the Middle East, especially Saudi Arabia, higher prevalence of MPS type I was observed compared to reported rates from European countries and the United States (U.S). The present work was developed as a part of the Saudi MPS Group’s efforts to address the current situation of MPS type I in Saudi Arabia and to reach a national consensus in the management of MPS type I. The first “Management of MPS Type I Advisory Board” meeting was held in Riyadh on May 2, 2019, to reflect the expert opinions regarding different aspects of MPS type I and develop this manuscript; eight consultants from different specialties (medical genetics, pediatric rheumatology, and pediatric endocrinology), representing six Saudi institutions, in addition to a global expert in genetics participated in the meeting.

Introduction
Glycosaminoglycans (GAGs) are long unbranched polysaccharides that result from the degradation of proteoglycans and undergo intracellular digestion inside the lysosome [1]. To date, 10 known enzymes participate in the lysosomal degradation of GAGs through four different pathways [2]. The deficiency in the α-L-iduronidase (IDUA) enzyme activity and the intracellular accumulation of dermatan and heparan sulfate lead to the development of mucopolysaccharidosis (MPS) type I; MPS type I is an autosomal recessive disorder with the progressive course and multisystem involvement [3]. MPS type I is one of the commonest types of MPS and accounts for up to 15% of the total cases of MPS [4]. Patients with MPS type I can present with characteristic facial features, cognitive and neurological impairment, hearing impairment, eye problems, cardiomyopathy and heart failure, recurrent respiratory infection, acute and chronic liver failure, joint contractures and cervical instability, and spinal stenosis [3]. In addition, patients with MPS type I are at higher risks of morbidity and mortality during anesthesia and surgical interventions [5].

In the Middle East, especially Saudi Arabia, higher prevalence of MPS type I was observed compared to reported rates from European countries and the United States (U.S) [6]. The high rate of consanguinity was postulated as the main contributing factors to this high incidence [7]. However, published data on the characteristics and treatment patterns of MPS patients in Saudi Arabia are still lacking.

The present work was developed as a part of the Saudi MPS Group’s efforts to address the current situation of MPS type I in Saudi Arabia and to reach
a national consensus in the management of MPS type I. The first “Management of MPS Type I Advisory Board” meeting was held in Riyadh on May 2, 2019, to reflect the expert opinions regarding different aspects of MPS type I and develop this manuscript; eight consultants from different specialties (medical genetics, pediatric rheumatology, and pediatric endocrinology), representing six Saudi specialized institutions, in addition to a global expert in genetics participated in the meeting. The consultants discussed different aspects of MPS type I management in Saudi Arabia and a consensus statement in each aspect was reached by the agreement of all attendants.

INCIDENCE OF MPS TYPE I IN SAUDI ARABIA

Arab world represents one of the leading regions in terms of the incidence of congenital and genetic disorders; a growing body of published literature reported a notable trend toward higher incidence of congenital and genetic diseases, compared to other parts of the world [8]. High consanguinity rates which reach up to 60% in some regions, high prevalence of hemoglobinopathies and metabolic disorders, relatively high maternal and parental age, and lack of proper genetic screening were reported as contributing factors for this high prevalence of genetic disorders in the Arab world [8], [9], [10]. In Saudi Arabia, the situation appears to be no different as previous retrospective studies showed a relatively high incidence of genetic diseases such as inborn error of metabolism, including MPS type I.

The first retrospective study, which reported the incidence of MPS in Saudi Arabia, utilized the data from the Saudi Aramco Medical Services Organization, which provides comprehensive health-care residents of the Eastern Province, was conducted. Out of 165,130 live births during this period, 248 cases had metabolic diseases with 28 of these cases which were MPSs. The most common type of MPS was type VI (48% of the total cases) with reported birth prevalence of 7.85 per 100,000 live births. The authors reported that the combined incidence of MPS I and MPS IV was 3.62/100,000 live births, and each accounted for 21% of all MPS. Finally, the birth prevalence of MPS III was 1.8/100,000 (11% of total cases) [6].

In addition, Al-Sannaa et al. performed a hospital-based retrospective analysis to evaluate the incidence of lysosomal storage disease (LSDs) in the Eastern Province of Saudi Arabia between 1983 and 2016. The incidence of MPSs was 14/100,000 live birth; with MPS VI represented the largest subtype [11]. Another 13-year retrospective chart review of all live birth at the Pediatric Department of King Abdulaziz Medical City was 14/100,000 live birth [12].

If we combined the incidence rate of MPS in the abovementioned studies, we can conclude that the incidence of MPS in Saudi Arabia is near 30 cases/100,000 live birth, which highlights the notable high prevalence of this LSDs in Saudi Arabia, compared to other parts of the world. The recent global figure shows that the overall birth prevalence of MPS ranges from 1.04 to 4.8/100,000 live births. For example, Khan et al. [4] retrospectively reviewed the number of live births with MPS in Switzerland between 1975 and 2008 (nearly similar to the study’s period of Moammar et al.); the results showed that the combined birth prevalence for diagnosed MPS was 1.56/100,000 live births. This incidence was quite similar to the reported incidences from Japan and other East Asian countries during the same period [13], [14], [15]. The incidence of MPS in Saudi Arabia appears to be even higher than those reported from other Arab countries; a previous report from Tunisia reported an MPS birth prevalence of 2.27/100,000 live births. However, MPS type I was the most common type of all MPSs (25%) with a birth prevalence of 0.63/100,000 live births [16].

However, the experts raised concerns about the generalizability of the published retrospective studies from Saudi Arabia on the total population of the Kingdom; the published reports included the live births from one institution or one district of the Kingdom. Therefore, there is a need for multicenter studies to reflect the real epidemiology of MPS in Saudi Arabia. Another concern is the lack of a nationwide newborn screening program, which could help to accurate the estimation of the incidence of MPS in Saudi Arabia.

Experts’ opinion

To date, there are no reliable data regarding the incidence of MPS type I in Saudi Arabia and future multicenter studies are needed. In addition, the prevalence of an attenuated form of MPS type I is largely underestimated in Saudi Arabia due to the absence of effective newborn screening program. Therefore, implementation of a nationwide newborn screening program is essential for accurate estimation of the burden of MPS and early diagnosis of the patients.

DIAGNOSIS OF MPS TYPE I IN SAUDI ARABIA

Newborn screening program for MPS type I

MPS type I is a chronic, progressive, disorder with multisystem affection and fatal disease course. Although patients with MPS type I usually present with very distinctive physical and cognitive features, most of
the patients with MPS are asymptomatic at birth [17]. Early diagnosis of MPS type I can potentially reduce disease progression and improve the quality of life of the patients; thus, newborn screening methods are promising modalities for optimizing the outcomes of MPS [18]. With the introduction and availability of tandem mass spectrometry (MS/MS) methods, it has become feasible to implement newborn screening programs for many metabolic disorders in both developed and developing countries. LSD screening programs have gained much attention recently and pilot LSD programs were conducted in a number of countries [19], [20]. These reports demonstrated that there are a number of feasible, effective, and affordable methods for LSD screening programs which can be extended to the larger population [21].

In the setting of MPS, different methods are available for early diagnosis of MPS type I, based on detection of the deficient enzyme activity, using dried blood spot punches. Conventional fluorimetric methods are one of the widely available techniques for the detection of enzymatic activity, however, it has limited value in testing multiple enzymes simultaneously [22]. MS/MS methods, which quantify the lysosomal enzyme activity, exhibited high diagnostic accuracy for the detection of LSD and high capacity for multiplex testing [23]. Recent reports have also introduced new, cheap, and feasible MS/MS-based methods for the mass detection of MPS type I [24], [25].

Such advances in the diagnostic methods have encouraged previous studies to conduct a number of MPS I neonatal screening programs, the aim of these studies was to evaluate the utility of MPS I neonatal screening for inclusion in primary screening programs. From 2008 to 2013, a pilot screening program for MPS type I was conducted on 35,286 newborns from Taiwan. Only two neonates had confirmed the diagnosis of MPS type I, the incidence in Taiwan estimated from this study is about 1/17,643 [26]. In the US, a number of states have conducted a pilot MPS screening program. In a comprehensive program for LSDs at Missouri, a multiplexing digital microfluidic screening program. In a comprehensive program for LSDs at Missouri, a multiplexing digital microfluidic fluorimetric enzymatic assay was used to detect Pompe disease, Fabry disease, Gaucher disease, and MPS I started in 2013. Out of 43,701 screened newborns, a total of three newborns had confirmed the diagnosis of MPS type I and seven newborns had pseudodeficiency. The incidence rate of 1:14,567 for MPS I is in the same range reported in a previous Taiwanese pilot study (1:17,643) [27]. Another important experience in a newborn screening program for LSD including MPS I has been reported in Illinois, USA. MS/MS was used to assay for the five LSD-associated enzymes to detect MPS I, Pompe disease, Fabry disease, Gaucher disease, and Niemann-Pick disease type A/B. Only one infant was confirmed with a positive diagnosis of MPS I and the incidence was therefore 1 in 219,793 newborns [28]. Based on these findings, the Recommended Uniform Screening Panel of the US Department of Health and Human Services Secretary’s Advisory Committee on Heritable Disorders in Newborns and Children includes Pompe and MPS I diseases in the primary panel for neonatal screening programs [18].

In Saudi Arabia, there is established national newborn screening program since 2005 that covers inborn error of metabolism, endocrine disorders, congenital heart defects, and hearing loss [29]. A recent 7-year retrospective study in 139 hospitals reported a high rate of inborn error of metabolism in Saudi Arabia compared to other parts of the world [30]. However, the inclusion of LSD, including MPS type I, in the program has not been discussed yet. The experts agreed that there is a need for LSD newborn screening program in Saudi Arabia that included MPS. However, the lack of reliable data about the incidence of MPS in Saudi Arabia is one of the main barriers against implementing such a program. One expert in our meeting suggested to start the newborn screening from the main three research centers in the Eastern provenance to provide data about the incidence rates of MPS; the results of such survey can open the window for implementation of nationwide screening program directed for MPS.

Diagnosis of MPS type I

The diagnosis of MPS type I depends on the detection of GAG in urine and significant deficiency in the activity of IDUA enzyme. In patients with suggestive clinical features, the urinary GAG level is evaluated; however, normal levels of urinary GAG do not rule out the diagnosis of MPS. Although many methods are available for the measurement of GAG concentration, dimethyl methylene blue is one of the standard tests for the quantification of urinary GAG [17]. On the other hand, the identification of the type of accumulated GAG can be done using chromatography or electrophoresis [31]. Alongside biochemical analysis, the molecular tests play a critical role in the identification of the genotype of MPS; knowing the genotype could potentially aid in the identification of the phenotype, genetic counseling, and prenatal diagnosis [32].

The experts stated that only a few institutions in Saudi Arabia provide urinary GAG measurements and many samples are sent abroad for assessment. This can increase the risk of false results due to malpractice during handling and transportation.

Experts’ Opinion

There are a lot of local barriers for newborn screening in Saudi Arabia. The main barrier is the lack of clear data about the incidence rate. Therefore, there is a need to provide reliable data about the incidence of MPS type I before implementing newborn screening of MPS in Saudi Arabia. The availability of treatment for
MPS is critical in making newborn screening effective. Health-care providers may play a role in providing the treatment at an affordable cost in different centers in Saudi Arabia. The experts also agreed that there is a need for Saudi consensus regarding the diagnosis and treatment of MPS in Saudi Arabia. The consensus should be comprehensive and involve all specialties that deal with MPS to share their ideas and suggestions. All key players must be invited to this type of meeting. The meeting can be conducted in the form of national MPS day. Another interesting idea is to develop a national day for rare disease in which experts get together and hence move forward.

Management of MPS Type 1 in Saudi Arabia

Ideally, effective treatment of MPS type I should be able to prevent the intracellular accumulation of GAG, slow disease progression, and restore enzyme activities. There are few treatment options available for the management of MPS type 1. In the early 1980s, hematopoietic stem cell transplantation (HSCT) was introduced for the treatment of MPS type I, especially infants with Hurler syndrome [33]. The previous reports have shown that early introduction of HSCT before the age of two can significantly prolong patients’ survival and slow neurological deterioration [34]. However, HSCT is an invasive procedure with a high risk of mortality and morbidity; thus, only severe cases are candidates for HSCT [35].

More recently, enzyme replacement therapy (ERT) with laronidase (Aldurazyme®, BioMarin Pharmaceutical, and Genzyme, a Sanofi Company) has emerged as a promising modality for MPS management. In 2003, the laronidase was the first ERT to be approved for the management of MPS type I without neurological involvement, as weekly intravenous infusion [36]. Conventional ERT has been approved in many countries, including the United States, Canada, EU, and Japan, as a treatment option for patients who have a confirmed diagnosis of MPS I. Clinical studies and case reports showed a significant reduction in urinary GAG and liver volume after laronidase treatment, however, the impact of treatment on cardiac or respiratory involvement [37]. Alongside these two options, patients may benefit from symptomatic and supportive therapy such as surgical intervention and speech therapies [36].

Recently, gene therapy was introduced as one of the promising options for many inherited diseases including MPS. The modality is based on delivering the defective gene to the affected cells through a specific vector or injection [38]. As CNS involvement appears to be resistant for ERT, current research for gene therapy is mainly directed at the neurocognitive and musculoskeletal levels [39]. Other novel experimental therapies for MPS include substrate reduction therapy, anti-inflammatory therapy, and pharmacological chaperone therapy.

Conclusions and Recommendations

a. There are no reliable data regarding the incidence of MPS type I in Saudi Arabia, future multicenter studies are needed
b. The prevalence of an attenuated form of MPS type I is underestimated in Saudi Arabia

Experts’ opinion

There is a need for global effort to provide affordable drugs for patients with MPS. The Saudi ministry of health can negotiate with pharmaceutical companies to provide the ERT at affordable price, even as part of an insurance plan.

Discussion

Saudi Arabia is the largest country in the Arabian peninsula, with a population of more than 28 million [40]. Despite health care being free to Saudi citizens, a number of potential barriers to health-care access and individual health-care seeking have been reported [41], [42]. While MPS is a rare disease, its incidence in Saudi Arabia appears to be higher than other parts of the world. Nevertheless, no previous nationwide study was conducted to provide reliable data regarding the incidence and characteristics of Saudi patients with MPS. There is a scarcity in the published literature regarding the treatment patterns and outcomes of MPS in Saudi Arabia as well.

The Saudi MPS Group’s held a consensus meeting to gather views from a panel of Saudi experts on current trends and practice regarding MPS in Saudi Arabia and to compare their views with current global trends and practice. Panel members highlighted the need for a central, unified, and updated national registry to monitor the current trends of MPS in the Kingdom.

Although uGAG measurement and molecular testing were considered an essential diagnostic tool by the panel members, many Saudi health-care facilities do not have access to uGAG tests and many samples are sent abroad for testing; thus, average time for MPS diagnosis and referral from first presentation may be prolonged with high possibility of false results due to malpractice during sample handling and transportation. Issues around the availability of drugs and their costs have been also raised by the experts. Finally, the panel members recommended the development of educational and quality improvement programs to improve physician’s knowledge and awareness about MPS.
c. There is a need to increase the awareness among the primary care physicians and pediatricians about MPS, particularly the attenuated form.

d. Early diagnosis is critical for patients with MPS type I to effectively slow down disease progression.

e. There is a need to provide reliable data about the incidence of MPS type I before implementing newborn screening of MPS in Saudi Arabia.

f. The availability of treatment for MPS is critical in making newborn screening effective.

g. There is a need for Saudi consensus regarding the diagnosis and treatment of MPS in the kingdom.

h. The consensus should be comprehensive and involve all specialties that deal with MPS to share their ideas and suggestions. All key players must be invited to this type of meeting. The meeting can be conducted in the form of national MPS day.

i. There is a need for a national day for rare diseases in which experts can gather, interact together, share their experiences, and discuss the recent updates.

j. There is a need for global efforts to provide affordable drugs for patients with MPS. The Saudi ministry of health can negotiate with pharmaceutical companies to provide drugs with affordable prices, even as a part of an insurance plan.

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References

1. Zhang L. Glycosaminoglycan (GAG) biosynthesis and GAG-binding proteins. In: Progress in Molecular Biology and Translational Science. United States: Academic Press; 2018. p. 1-17. https://doi.org/10.1016/s1877-1173(10)93001-9

2. Dorfman A, Mataloni A. The mucopolysaccharidoses (a review). Proc Natl Acad Sci U S A. 1976;73(2):630-7. PMid:813230

3. Giugliani R, Federhen A, Rojas MV, Vieira T, Artigalás O, Pinto LL, et al. Mucopolysaccharidosis I, II, and VI: Brief review and guidelines for treatment. Genet Mol Biol. 2010;33(4):589-604. PMid:21637564

4. Khan SA, Peracha H, Ballhausen D, Wiesbauer A, Rohrbach M, Gautschi M, et al. Epidemiology of mucopolysaccharidosis. Mol Genet Metab. 2017;121(3):227-40. PMid:28595941

5. Ard JL, Bekker A, Frempong-Boadu AK. Anesthesia for an adult with mucopolysaccharidosis I. J Clin Anesth. 2005;17(8):624-6. https://doi.org/10.1016/j.jclinane.2005.01.012

6. Moammar H, Cherian G, Mathew R, Al-Sannaab N. Incidence and patterns of inborn errors of metabolism in the Eastern Province of Saudi Arabia, 1983-2008. Ann Saudi Med. 2010;30(4):271-7. https://doi.org/10.4103/0326-4947.65254 PMid:20622343

7. Bittles AH. The role and significance of consanguinity as a demographic variable. Popul Dev Rev. 2006;20:561.

8. Al-Gazzi L, Hamamy H, Al-Arrayad S. Genetic disorders in the Arab world. BMJ. 2006;333(7573):831-4. https://doi. org/10.1136/bmj.38982.704931.ae

9. Al-Gazzi LI, Alwash R, Abdurrazzaq YM. United Arab Emirates: Communities and community genetics. Community Genet. 2005;8(3):186-96. https://doi.org/10.1159/000086764

10. Wahab AA, Bener A, Teebi AS. The incidence patterns of down syndrome in Qatar. Clin Genet. 2006;69(4):360-62. https://doi.org/10.1111/j.1399-0004.2006.00593.x

11. Al-Sannaab NA, Al-Abdulwahed HY, Al-Chamidi MS. Lysosomal storage disorders (LSDs): The prevalence in the Eastern Province of Saudi Arabia. Int J Neurol Dis. 2017;1(2):38-43.

12. Alfares AA, Bennakeel M, Hossain MA, Al Mutairi F, Al Ostham I, Alfares AA, et al. Thirteen year retrospective review of the spectrum of inborn errors of metabolism presenting in a tertiary center in Saudi Arabia. Orphanet J Rare Dis. 2016;11:126. https://doi.org/10.1186/s13023-016-0510-3

13. Lin HY, Lin SP, Chuang CK, Niu DM, Chen MR, Tsai FJ, et al. Incidence of the mucopolysaccharidoses in Taiwan, 1984-2004. Am J Med Genet Part A. 2009;149(5):960-4. https://doi.org/10.1002/ajmg.a.32781

14. Cho SY, Sohn YB, Jin DK. An overview of Korean patients with mucopolysaccharidosis and collaboration through the Asia Pacific MPS Network. Intractable Rare Dis Res. 2014;3(3):79-86. https://doi.org/10.5582/irdr.2014.01013

15. Chen X, Qiu W, Ye J, Han L, Gu X, Zhang H. Demographic characteristics and distribution of lysosomal storage disorder subtypes in Eastern China. J Hum Genet. 2016;61(4):345-9. https://doi.org/10.1038/jhmg.2015.185

16. Ben Turlia H, Tebib N, Azzouz H, Abdelmoula MS, Chehida AB, Chemli J, et al. Incidence of mucopolysaccharidoses in Tunisia. Tunis Med. 2009;87(11):782-5. PMid:19396827

17. Cho SY, Sohn YB, Jin DK. An overview of Korean patients with mucopolysaccharidosis and collaboration through the Asia Pacific MPS Network. Intractable Rare Dis Res. 2014;3(3):79-86. https://doi.org/10.5582/irdr.2014.01013

18. Donati MA, Pasquini E, Spada M, Polo G, Burfina A. Newborn screening in mucopolysaccharidosis. Ital J Pediatr. 2018;44(2):126. https://doi.org/10.1186/s13052-018-0552-3 PMid:30442156

19. Peake R, Bodamer O. Newborn screening for lysosomal
storage disorders. J Pediatr Genet. 2016;6:51-60. https://doi.org/10.1055/s-0036-1593843

20. Anderson S. Newborn screening for lysosomal storage disorders. J Pediatr Health Care 2018;32(3):285-94. PMid:29678259

21. Paciotti S, Persichetti E, Pagliardini S, Degano M, Rosano C, Balducci C, et al. First pilot newborn screening for four lysosomal storage diseases in an Italian region: Identification and analysis of a putative causative mutation in the GBA gene. Clin Chim Acta. 2012;413(23-24):1827-31. https://doi.org/10.1016/j.cca.2012.07.011 PMid:22820396

22. Sista RS, Wang T, Wu N, Graham C, Eckhardt A, Winger T, et al. Multiplex newborn screening for Pompe, Fabry, Hunter, Gaucher, and hurler diseases using a digital microfluidic platform. Clin Chim Acta. 2013;424:12-8. https://doi.org/10.1016/j.cca.2013.05.001 PMid:23660237

23. Duffey TA, Bellamy G, Elliott S, Fox AC, Glass M, Turecek F, et al. Diagnosis and treatment trends in mucopolysaccharidosis I: Findings from the MPS I registry. Eur J Pediatr. 2012;171(6):911-9. https://doi.org/10.1007/s00431-011-1644-x PMid:22234477

24. Elliott S, Buroker N, Courmoyer JJ, Potier AM, Trometer JD, Elbin C, et al. Pilot study of newborn screening for six lysosomal storage diseases using tandem mass spectrometry. Mol Genet Metab. 2016;118(4):304-9. https://doi.org/10.1016/j.mgme.2016.05.015 PMid:22738910

25. Van Malderen L, Keraans A, Boelens JJ, Moraine J, Bertrand Y, Rajab A, et al. Pilot study of newborn screening for mucopolysaccharidoses Type I in Taiwan. Orphanet J Rare Dis. 2013;8:147. https://doi.org/10.1186/1750-1172-8-147 PMid:24053568

26. Burton BK, Charrow J, Hoganson GE, Waggoner D, Tinkle B, Braddock SR, et al. Newborn screening for lysosomal storage disorders in Illinois: The initial 15-month experience. J Pediatr. 2017;190:130-5. https://doi.org/10.1016/j.jpeds.2017.06.048 PMid:28728811

27. Hopkinson P, Campbell C, Kug T, Rogers S, Raburn-Miller J, Kiesling J, et al. Lysosomal storage disorder screening implementation: Findings from the first six months of full population pilot testing in Missouri. J Pediatr. 2015;166(1):172-7. https://doi.org/10.1016/j.jpeds.2014.09.023 PMid:25444528

28. Burton BK, Charrow J, Hoganson GE, Waggoner D, Tinkle B, Braddock SR, et al. Newborn screening for lysosomal storage disorders in Illinois: The initial 15-month experience. J Pediatr. 2017;190:130-5. https://doi.org/10.1016/j.jpeds.2017.06.048 PMid:28728811

29. Gosadi IM. National screening programs in Saudi Arabia: Overview, outcomes, and effectiveness. J Infect Public Health. 2019;12(5):808-14. https://doi.org/10.1016/j.jiph.2019.06.001 PMid:31248815

30. Alkadhi M, Al Othaim A, Al Saff S, Al Mutairi F, Alsayed M, Rahbeeni Z, et al. Expanded newborn screening program in Saudi Arabia: Incidence of screened disorders. J Paediatr Child Health. 2017;53(6):585-91. https://doi.org/10.1111/jpc.13469 PMid:28337809

31. Leistner S, Giugliani R. A useful routine for biochemical detection and diagnosis of mucopolysaccharidoses. Genet Mol Biol. 1996;21(1):163-7. https://doi.org/10.1590/s1415-475719980000100028

32. Pastores GM, Am P, Beck M, Clarke JT, Guuffman N, Kaplan P, et al. The MPS I registry: Design, methodology, and early findings of a global disease registry for monitoring patients with mucopolysaccharidosis Type I. Mol Genet Metab. 2007;91(1):37-47. https://doi.org/10.1016/j.ymgme.2007.01.011 PMid:17336562

33. Aldenhoven M, Boelens J, de Koning TJ. The clinical outcome of hurler syndrome after stem cell transplantation. Biol Blood Marrow Transplant. 2008;14(5):485-98. https://doi.org/10.1016/j.bbmt.2008.01.009 PMid:18410891

34. Muenzer J, Wraith JE, Clarke LA. Mucopolysaccharidosis I: Management and treatment guidelines. Pediatrics. 2009;123(1):19-29. https://doi.org/10.1542/peds.2008-0416 PMid:19117856

35. Boelens JJ, Wynn RF, O’Meara A, Veys P, Bertrand Y, Soullet G, et al. Outcomes of hematopoietic stem cell transplantation for Hurler’s syndrome in Europe: A risk factor analysis for graft failure. Bone Marrow Transplant. 2007;40(3):225-33. https://doi.org/10.1038/sj.bmt.1705718 PMid:17529997

36. D’Aco K, Underhill L, Rangachari L, Arn P, Cox GF, Giugliani R, et al. Diagnosis and treatment trends in mucopolysaccharidosis I: Findings from the MPS I registry. Eur J Pediatr. 2012;171(6):911-9. https://doi.org/10.1007/s00431-011-1644-x PMid:22234477

37. Pérez-López J, Morales-Conejo M, López-Rodríguez M, Hermina-Ameijeiras A, Moltó-Abad M. Efficacy of laronidase therapy in patients with mucopolysaccharidosis Type I who initiated enzyme replacement therapy in adult age. A systematic review and meta-analysis. Mol Genet Metab. 2017;121(2):138-49. https://doi.org/10.1016/j.molgenetb.2017.04.004 PMid:28410878

38. Yokoi K, Akiyama K, Kaneshiro E, Higuchi T, Shimada Y, Kobayashi H, et al. Effect of donor chimerism to reduce the level of glycosaminoglycans following bone marrow transplantation in a murine model of mucopolysaccharidosis Type II. J Inherit Metab Dis. 2015;38:333-40. https://doi.org/10.1007/s10545-014-9800-x PMid:25503568

39. Fraldi A, Serafini M, Sorrentino NC, Gentner B, Aiuti A, Bernardo ME, et al. Gene therapy for mucopolysaccharidoses: In vivo and ex vivo approaches. Ital J Pediatr. 2018;44(2):130. https://doi.org/10.1186/s13052-018-0565-y PMid:30442177

40. Saudi Ministry of Health. Health Statistical Year Book 2015. Saudi Arabia: Saudi Ministry of Health; 2015. p. 28-49.

41. Alkhams A. Health care system in Saudi Arabia: An overview. East Mediterr Health J. 2012;18:1078-9. https://doi.org/10.26719/2012.18.10.1078

42. El Bcheraoui C, Tuffaha M, Daoud F, Kravitz H, AlMazroa MA, Al Saeed M, et al. Access and barriers to healthcare in the Kingdom of Saudi Arabia, 2013: Findings from a national multistage survey. BMJ Open. 2015;5(6):e007801. https://doi.org/10.1136/bmjopen-2015-007801 PMid:26070798