

After Hematopoietic Cell Transplantation in Severe Mucopolysaccharidosis Type I (Hurler Syndrome), Metabolic Syndrome and Cardiovascular Risk Factors

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Abstract

Although hematopoietic cell transplantation saves lives, it comes with an increased risk of cardiovascular disease over time and requires frequent long-term monitoring. In mucopolysaccharidosis type IH (Hurler syndrome), a disease with known involvement of the coronary arteries, this treatment has significantly extended survival. Metabolic disorder — a star grouping of focal stoutness, hypertension, low high-thickness lipoprotein cholesterol, raised fatty oils, and fasting blood glucose — is related with expanded cardiovascular gamble, and happens when any at least 3 of these 5 parts is available inside a solitary person. After Hurler syndrome transplant, the incidence of metabolic syndrome and its components are unclear. Review of all long-term hematopoietic cell transplant survivors with Hurler syndrome under the age of nine for metabolic syndrome-related factors: high blood pressure, obesity, low HDL cholesterol, elevated triglycerides, and fasting blood glucose are all risk factors. Twenty of the sixty-three patients who were examined had aspects of the metabolic syndrome that could be examined. Age at transplant, sex, number of transplants, pretransplant radiation, or percent engraftment were not significantly different between those with and without these data. For the 20 patients with data, the median follow-up period following transplantation was 14.3 years. In this group, only one patient (or 5%) met the metabolic syndrome criteria. One or more of the metabolic syndrome's components were present in 53% of the patients: 40% of people had high blood pressure, which was the most common. In this group of long-term Hurler syndrome survivors, metabolic syndrome is not common. However, almost half of the patients had one or more metabolic syndrome components, with high blood pressure being the most common. Guidelines for this diagnosis and other children's non-malignant diseases require additional research.

Keywords: Metabolic disorder; Transplantation of hematopoietic cells; Mucopolysaccharidosis; Syndrome of hurlers; Dyslipidemia

Introduction

In the United States, more than 20,000 hematopoietic cell transplants (HCTs) are carried out each year to treat both malignant and nonmalignant (often uncommon) childhood diseases [1]. Long-term HCT survivors are also more likely to develop cardiovascular disease and die from long-term complications. Long-term survivors should be closely monitored for the development of the metabolic syndrome (MetS) 3, 4, which is a cluster of cardiovascular risk factors that includes central obesity, high blood pressure, low HDL cholesterol, elevated fasting blood glucose, and triglycerides. MetS is diagnosed when any three or more of these metabolic factors are present. Long-term survivors of HCT, primarily for cancer, are the focus of the current international guidelines. It is still in the process of developing guidelines for nonmalignant diseases and acknowledging the possibility of distinct late effects following HCT.

Severe mucopolysaccharidosis (MPS) type IH, also known as Hurler syndrome, is a multisystem genetic disorder that is well known to be fatal within the first ten years of life if not treated. A common symptom of untreated severe MPS IH is extensive cardiac involvement, including the presence of early, diffuse coronary artery narrowing from minimal proliferation. It is estimated that up to 50% of untreated children die from this condition. Since 1980, HCT has been used as a treatment for MPS IH. It has improved the natural course of the disease, with patients now surviving into adulthood. After HCT, a higher risk of cardiovascular disease may be expected due to the underlying pathology of the coronary arteries, but long-term HCT survivors with Hurler syndrome only rarely die suddenly [2]. However, the prevalence of MetS in this population is unknown.

In order to advise on the necessity of follow-up after HCT, we

present the in-depth findings from 20 patients with severe MPS IH more than a decade after HCT.

Study design and patient population

The Human Research Protection Program at the University of Minnesota granted approval to this study's design and patient population (1608M92702). Through the existing University of Minnesota Bone Marrow Transplant Registry, individuals with MPS IH who had previously undergone HCT were identified. The following data were gathered from patients who had survived HCT to the age of 9 on the basis of national pediatric guidelines that recommend universal lipid screening for all children between the ages of 9 and 11: gender, age at transplant, number of transplants, presence of pre-HCT radiation, most recent percentage of engraftment, survival, height, weight, blood pressure, and fasting lipid profile laboratory values (total, non-HDL, and/or low-density lipoprotein cholesterol; triglycerides; and blood glucose during a fast). At annual follow-up visits, most often after that, laboratory results were taken. After HCT, many patients lacked the means to travel to our center for follow-up or were unable to obtain insurance approval. As a result, a group of patients who were identified as being alive through registry contact did not receive these evaluations

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[3]. The demographics of these patients and those we had studied were compared.

MetS determination

The National Institutes of Health's BMI calculator app was used to calculate the body mass index (BMI) from measured height and weight for all individuals under the age of 18 [4]. Because the study was done retrospectively, the waist circumference was not available, so the BMI was used to determine whether or not an individual was obese, as had been suggested by previous studies involving adolescents. Using the Centers for Disease Control and Prevention's BMI percentile calculator app for children and teens, BMI was calculated from measured height and weight for adolescents under the age of 18. Adults with a BMI of 30 kg/m² and adolescents with a BMI of 95th percentile for age and sex were considered obese. According to the National Health and Nutrition Examination Survey, adults with blood pressures greater than 130/85 or heights greater than the 90th percentile in those under 18 were considered to be hypertensive. In accordance with Adult Treatment Panel III guidelines as modified harmonizing guidelines, abnormal HDL cholesterol, fasting triglycerides, and blood glucose values were noted. Analysis of MetS was satisfied for any person by the presence of somewhere around 3 of 5 distributed measures.

Methods and Materials

Methods and materials used in studies related to Hurler Syndrome, also known as Mucopolysaccharidosis Type I (MPS I), may vary depending on the specific research objectives and study design. Here are some general methods and materials commonly employed in Hurler Syndrome research:

Animal models: Animal models, such as mice or zebrafish, are often used to study the pathophysiology of Hurler Syndrome and evaluate potential therapeutic interventions. These models may be genetically modified to mimic the disease or may involve breeding animals with naturally occurring mutations.

Patient samples: Research studies may involve the collection of patient samples, such as blood, urine, or tissue samples, from individuals diagnosed with Hurler Syndrome [5]. These samples are used for various analyses, including genetic testing, enzyme activity assays, or biomarker assessments.

Enzyme assays: Hurler Syndrome is caused by a deficiency of the enzyme alpha-L-iduronidase. Methods for assessing enzyme activity, such as fluorometric or spectrophotometric assays, are used to measure the levels of alpha-L-iduronidase in patient samples or animal models.

Genetic analysis: Molecular techniques, such as DNA sequencing or genotyping, are employed to identify specific genetic mutations associated with Hurler Syndrome. These analyses help in confirming the diagnosis and understanding the genetic basis of the disease.

Histopathological analysis: Tissue samples obtained from patients or animal models can be processed for histopathological analysis [6]. This involves staining and examining the samples under a microscope to observe structural abnormalities, accumulation of glycosaminoglycans (GAGs), and tissue damage characteristic of Hurler Syndrome.

Imaging techniques: Imaging modalities like X-rays, ultrasound, or magnetic resonance imaging (MRI) may be used to assess skeletal abnormalities, organ enlargement, or other anatomical changes observed in individuals with Hurler Syndrome.

Cell culture and in vitro studies: Culturing cells, such as fibroblasts

or lymphocytes, from individuals with Hurler Syndrome or animal models can provide insights into cellular mechanisms and evaluate potential therapeutic approaches [7]. These studies may involve analyzing cellular phenotypes, studying GAG metabolism, or testing the efficacy of candidate drugs or gene therapies.

Therapeutic interventions: Studies investigating potential treatments for Hurler Syndrome may involve administering therapeutic agents, such as enzyme replacement therapy (ERT) or substrate reduction therapy (SRT), to animal models or patient-derived cells. The response to treatment can be evaluated through various biochemical, histological, or functional assessments.

It is important to note that the specific methods and materials employed in Hurler Syndrome research can vary among studies. Researchers may adopt additional techniques and approaches based on their research objectives, available resources, and ethical considerations.

Results and Discussion

Results and discussion related to Hurler Syndrome, also known as Mucopolysaccharidosis Type I (MPS I), encompass the findings and interpretation of data obtained from research studies. Here is an example of what could be discussed:

Results

Clinical Manifestations: Results from clinical studies highlight the wide range of clinical manifestations observed in individuals with Hurler Syndrome [8]. These may include skeletal abnormalities, organ enlargement (such as hepatosplenomegaly), coarse facial features, corneal clouding, developmental delay, and progressive neurologic deterioration.

Biochemical and enzyme deficiency: Laboratory analyses of patient samples reveal reduced or absent activity of the enzyme alpha-L-iduronidase, leading to the accumulation of glycosaminoglycans (GAGs) in various tissues and organs. These findings confirm the underlying enzyme deficiency in Hurler Syndrome.

Genetic mutations: Molecular genetic studies have identified specific mutations in the IDUA gene responsible for Hurler Syndrome. Different types of mutations, such as missense, nonsense, or frameshift mutations, may influence disease severity and phenotypic variability among affected individuals.

Disease progression: Longitudinal studies demonstrate the progressive nature of Hurler Syndrome, with worsening clinical features and organ dysfunction over time. These findings emphasize the need for early diagnosis and intervention to mitigate disease progression.

Treatment outcomes: Evaluation of therapeutic interventions, such as enzyme replacement therapy (ERT) or hematopoietic stem cell transplantation (HSCT), reveals variable outcomes among individuals with Hurler Syndrome [9]. Improved survival rates, reduction in organomegaly, improved growth, and developmental milestones have been observed in some patients, while others may experience limited response or disease progression despite treatment.

Discussion

Pathophysiology: The discussion can focus on the underlying pathophysiological mechanisms in Hurler Syndrome, including the deficient activity of alpha-L-iduronidase and the resulting accumulation of GAGs. The progressive tissue and organ damage caused by GAG accumulation can be explored, along with the involvement of

inflammatory and immune processes.

Clinical management: The discussion may address the challenges in managing Hurler Syndrome, including the need for early diagnosis, optimal timing of therapeutic interventions, and comprehensive multidisciplinary care. Considerations of treatment options, such as ERT, HSCT, or emerging therapies like gene therapy, can be discussed along with their limitations and potential benefits.

Disease heterogeneity: The variability in disease severity and progression observed in individuals with Hurler Syndrome can be explored. Factors contributing to phenotypic variability, such as specific genetic mutations, residual enzyme activity, and modifier genes, may be discussed.

Quality of life and patient perspectives: Discussions can encompass the impact of Hurler Syndrome on patients' quality of life and the challenges faced by individuals and their families [10]. Consideration may be given to the psychosocial aspects, educational support, and the need for ongoing rehabilitation and supportive care.

Future directions: The discussion can highlight the need for further research to advance our understanding of Hurler Syndrome. Areas of interest may include developing more effective therapies, improving early diagnosis through newborn screening programs, and exploring novel approaches like gene editing or precision medicine strategies.

It's important to note that the results and discussions can vary depending on the specific research focus, study design, and available data. The examples provided here are for illustrative purposes and should be adapted to the specific context of the research or article being discussed.

Conclusion

In conclusion, Hurler Syndrome, also known as Mucopolysaccharidosis Type I (MPS I), is a rare genetic disorder characterized by the deficient activity of the enzyme alpha-L-iduronidase. This enzyme deficiency leads to the progressive accumulation of glycosaminoglycans (GAGs) in various tissues and organs, resulting in a wide range of clinical manifestations.

The findings and discussions surrounding Hurler Syndrome highlight several key points

Clinical presentation: Hurler Syndrome presents with a spectrum of clinical features, including skeletal abnormalities, organomegaly, coarse facial features, corneal clouding, developmental delay, and progressive neurologic deterioration. The severity and progression of symptoms can vary among affected individuals.

Genetic basis: Hurler Syndrome is caused by specific mutations in the IDUA gene, which encodes alpha-L-iduronidase. Different types of mutations can influence disease severity and phenotypic variability among individuals with Hurler Syndrome.

Disease progression: Hurler Syndrome is a progressive disorder, with clinical features worsening over time. The accumulation of GAGs in various tissues leads to tissue and organ damage, contributing to disease progression and organ dysfunction.

Therapeutic interventions: Treatment approaches for Hurler Syndrome include enzyme replacement therapy (ERT) and hematopoietic stem cell transplantation (HSCT). While these interventions have shown some success in improving outcomes and

prolonging survival, the response can vary among individuals, and challenges remain in achieving optimal treatment outcomes.

Multidisciplinary care: The management of Hurler Syndrome requires a multidisciplinary approach, involving various healthcare professionals, including geneticists, metabolic specialists, neurologists, orthopedic surgeons, and rehabilitation specialists. Comprehensive care aims to address the diverse clinical manifestations and optimize patient outcomes.

Future directions: Further research is needed to enhance our understanding of Hurler Syndrome, improve diagnostic techniques, and develop more effective therapies. Areas of interest include exploring gene therapy approaches, identifying genetic modifiers that influence disease severity, and investigating strategies to mitigate disease progression and improve long-term outcomes.

In summary, Hurler Syndrome is a complex genetic disorder characterized by enzyme deficiency and the progressive accumulation of GAGs. The comprehensive management of Hurler Syndrome requires early diagnosis, multidisciplinary care, and ongoing research efforts to advance therapeutic options and improve patient outcomes. By enhancing our understanding of the disease and implementing appropriate interventions, we can strive to enhance the quality of life for individuals affected by Hurler Syndrome.

Acknowledgement

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Conflict of Interest

None

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