American Journal of
Biomedical Science & Research

www.biomedgrid.com
ISSN: 2642-1747

Letter to Editor

Recent Research in Hurler Disease (MPS I) in Childhood

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To Cite This article: *Stefan Bittmann*, Elisabeth Luchter and Elena Moschüring-Alieva, Recent Research in Hurler Disease (MPS I) in Childhood. Am J Biomed Sci & Res. 2026 30(5) AJBSR.MS.ID.003965,* **DOI:** 10.34297/AJBSR.2026.30.003965

Received: March 30, 2026; **Published:** April 06, 2026

Letter to the Editor

Hurler syndrome is the most severe form of the rare metabolic disorder mucopolysaccharidosis type 1, caused by an enzyme deficiency that prevents the breakdown of certain sugars, leading to the accumulation of dermatansulfate and heparansulfate in tissues [1,2]. The gene defect is located at chromosome 4p16.3 gene locus. The incidence is 1:145.000 respectively. It is a monogenetic disease with an autosomal recessive trait. The gene defect leads to an enzyme defect of the enzyme alpha-L-iduronidase (IDUA) with the result of extensive accumulation of glycosaminoglycanes in different cell tissues [3,4]. Newborn screening detection is crucial for therapy success, especially for neuroprotection [3]. There are 3 different forms of Hurler disease. Morbus Hurler shows a serious involvement of the CNS, Morbus Hurler-Scheie an attenuated form with an incidence of 1:280000, and Morbus Scheie, which is found in 1:500000 newborns, shows only a moderate form of the disease [5-8]. Typical symptoms include coarse facial features, skeletal changes, enlarged organs with heptoslenomegaly, heart and breathing problems, and intellectual disabilities due to central nervous system involvement [9,10]. Early diagnosis and specialized therapies such as stem cell transplantation are important, but the prognosis is often limited due to the severity of the condition [11,12]. The challenge treating the disease in childhood is delivering sufficient enzymes to the brain to ameliorate the cognitive brain development by accumulation of GAG in the brain cells [13-15]. Recent research is focusing on next generation enzyme replacement therapies with crossing the blood-brain-barrier, HSCT, targeting nonsense mutations at mRNA level through nonsense suppression and mRNA editing suppressor t`RNA`s, in vivo and ex vivo gene transfers [16-20].

In Europe, the prevalence of the Hurler subtype of MPS1 is estimated at 1/200,000. The main features of Hurler syndrome are skeletal deformities and delayed motor and intellectual development. Patients typically present in the first year of life with changes in the musculoskeletal system: short stature, dysostosis multiplex, thoracolumbar kyphosis, progressive coarsening of facial features, large head, frontal bossing, flat nasal bridge with broad nasal tip and anteverted nares, full cheeks, widened lips, cardiomyopathy with valve abnormalities, sensorineural hearing loss, enlarged tonsils and adenoids, nasal discharge. Developmental delay becomes apparent between 12 and 24 months, especially in the area of speech, followed by progressive cognitive and sensory decline. Hydrocephalus may develop in some patients by age 2 [21]. By age 3, diffuse corneal changes progress to corneal opacification. Organomegaly, hernias, and hirsutism are additional symptoms. Hurler syndrome is caused by mutations in the IDUA gene, leading to complete loss of alpha-L-iduronidase activity and lysosomal storage of Dermatan Sulfate (DS) and Heparan Sulfate (HS). Hurler syndrome is inherited in an autosomal recessive manner. Early diagnosis is challenging as the initial clinical signs are nonspecific. However, early diagnosis is crucial for initiating treatment as soon as possible. Laboratory diagnosis involves detecting increased excretion of HS and DS in urine using the DMB test and GAG electrophoresis, as well as demonstrating enzyme deficiency in leukocytes or fibroblasts. Molecular testing is available. Differential

diagnoses include the milder form of mucopolysaccharidosis type 1, Hurler-Scheie syndrome, although this form is associated with only mild cognitive impairment. Differential diagnoses also include mucopolysaccharidosis type 6 and type 2, and mucolipidosis type 2. Prenatal diagnosis is possible enzymatically or molecularly. Genetic counseling should be offered to affected families. Management is multidisciplinary. Hematopoietic Stem Cell Transplantation (HSCT) is the treatment of choice for patients with Hurler syndrome under 2.5 years (and selected patients over this age) as it can prolong survival, preserve neurocognition, and improve some somatic features. HSCT should be performed early in the disease course before developmental decline begins. Enzyme replacement therapy with laronidase is recommended for all Hurler patients and is a lifelong therapy that alleviates non-neurological symptoms. Early ERT has been shown to delay or even prevent the development of some clinical features of the disease. Additional management of Hurler syndrome is largely supportive and includes surgical interventions (e.g., adenotonsillectomy, hernia repair, ventriculoperitoneal shunt, heart valve replacement, carpal tunnel release, spinal decompression), physical therapy, occupational therapy, speech therapy, respiratory support like continuous positive airway pressure with oxygen supplementation, hearing aids, and medications for pain and gastrointestinal disturbances. Patients often succumb to the disease in the first decade due to respiratory and cardiac complications, but ERT and HSCT can improve life expectancy. The timing of diagnosis and initiation of treatment is a crucial factor for the success of HSCT and laronidase.

Until the age of about 2.5 years, bone marrow or hematopoietic stem cell transplantation is the treatment of choice for patients with M. Hurler. Through the transplantation of bone marrow from a suitable donor, the patient receives blood cells that can produce the enzyme alpha-L-iduronidase. These cells release some of the produced, intact enzyme into the environment, which can be taken up by other body cells and transported into their lysosomes. This allows the stored glycosaminoglycans to be broken down. However, transplantation can only positively influence cognitive development and life expectancy. HSCT cannot cure the disease. In patients with M. Hurler, enzyme replacement therapy is often used before or after bone marrow or hematopoietic stem cell transplantation. In this therapy, the defective enzyme is replaced by a biotechnologically produced form of the human enzyme, allowing the pathological storage of glycosaminoglycans to be broken down again. However, due to the blood-brain barrier, the enzyme replacement therapy does not reach the central nervous system, so this therapy cannot directly affect the cognitive and motor symptoms of M. Hurler. This can currently only be achieved through early stem cell transplantation. Before HSCT, enzyme replacement therapy can improve the overall condition of patients. Additionally, enzyme replacement therapy can support the transplantation and alleviate symptoms, as MPS I cannot be cured by HSCT. For M. Hurler patients who are diagnosed later than 2.5 years and for whom bone marrow or stem cell transplantation is no longer an option, enzyme replacement therapy is available to treat the non-neurological manifestations of the disease.

The future prospects for Hurler syndrome are improving due to therapy-specific advances, with gene therapy and next generation enzyme replacement therapy as well as early hematopoietic stem cell transplants being the main pillars that increase life expectancy and alleviate symptoms, even though a complete cure is still pending [22]. The key lies in early diagnosis to protect brain and skeletal development, which are currently the biggest challenges [23-26]. New biomarkers are under research in animal models [27,28]. Enzyme replacement therapy is based on providing the missing substance through recombinant enzymes, non-neurological symptoms are improved and quality of life is increased, but it does not cross the blood-brain barrier to date [23,29-37]. Hematopoietic Stem Cell Transplantation (HSCT) is focused on younger patients under 2.5 years, it can preserve neurocognitive development and extend life expectancy, and is the most effective method so far, although it carries risks and requires a donor search [38-40]. Treats specific complaints such as heart or breathing problems and improves daily life.

Gene therapy aims to directly correct the gene defect and has the potential to address the root cause of the disease, enabling more comprehensive treatments [21,41-52]. Nanovector research is of upmost importance to deliver a functioning enzyme into brain cells with crossing the blood brain barrier [53-58]. Further research focus on intranasal delivery of an AAV-vector gene delivery system [59-61]. Substrate reduction therapy aims to reduce the production of harmful substances. The combination of ERT with gene therapy or SRT is being researched to increase effectiveness and also reach the brain [62]. The biggest challenge is the CNS involvement, therefore overcoming the blood-brain barrier remains the biggest hurdle for ERT.

In conclusion, with innovative approaches such as gene therapy with AAV-vector gene-or enzyme delivery systems or CRISP/Cas9 therapy and improved stem cell transplantation procedures, there is increasing hope to better control the life-threatening aspects of Hurler syndrome and improve the quality of life, even though the path to a complete cure is not yet complete [63-65].

Acknowledgement

None.

Conflict of Interest

None.

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