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Postenzyme replacement therapy era for type 2 mucopolysaccharidosis

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Type 2 mucopolysaccharidosis (MPS), also called Hunter syndrome (MIM:309900), is a rare X-linked genetic disorder caused by mutation in the iduronate 2-sulfatase gene (*IDS*: 300823). The gene encodes for the lysosomal enzyme iduronate 2-sulfatase (I2S), which is responsible for degradation of the glycosaminoglycans (GAGs) heparin sulphate (HS) and dermatan sulphate (DS). Consequent accumulation of GAGs leads to pathologic changes in multiple organ systems.

Clinically, patients often present with dysmorphic facial features (Fig. 1), skeletal deformities, joint stiffness, and short stature. Other clinical manifestations include valvular heart disease and hypertrophic cardiomyopathy, obstructive sleep apnea due to airway obstruction, and variable neurologic deficits such as mild to profound mental retardation. Diagnosis of MPS includes analysis of urine GAGs, enzyme assay from leukocytes or culture fibroblasts, and gene analysis of the *IDS* gene. Before the era of enzyme replacement therapy (ERT), patients usually died during the second decade of life due to cardiopulmonary failure.

ERT with recombinant I2S [idursulfase (Elaprase, Shire Human Genetic Therapies, Inc, Lexington, MA, USA)] has been used in patients with type 2 MPS since 2006. Its chief value is in improving patient quality of life, with an increased 6-minute walking distance and improved range of motion of joints. ERT has also been found to decrease urinary GAG secretion and reduce disease severity with less hepatosplenomegaly and improved pulmonary function, such as in the predicted forced vital capacity. The disadvantages of ERT include the inconvenience of weekly infusions of the enzyme. Infusion-related reactions include headache, pruritus, and urticaria,

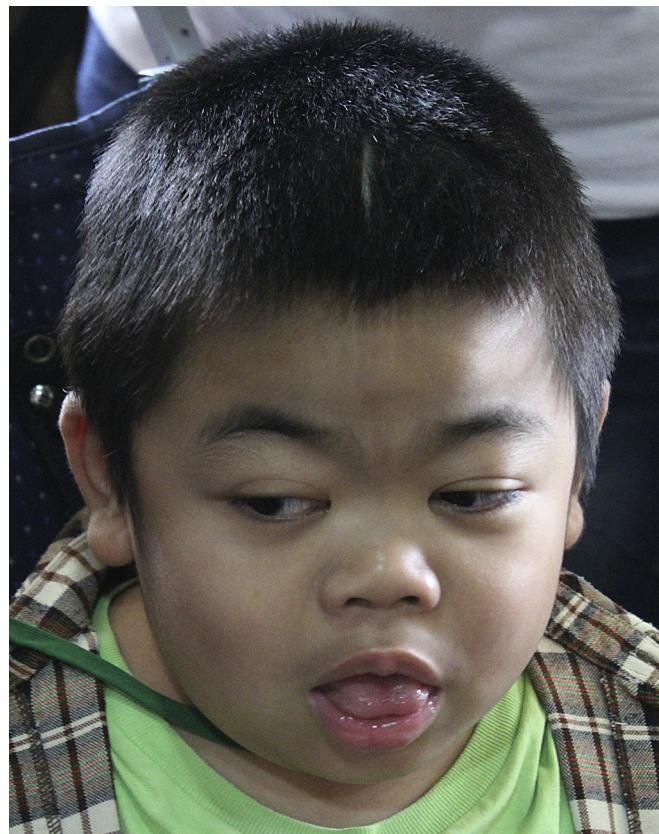


Fig. 1. Boy, 8 years of age with type 2 mucopolysaccharidosis who presented with macrocephaly, coarse hair, a short neck, a coarse, hairy face, puffy eyelids, depressed nasal bridge, upturned nose, macroglossia, full lips, and thick skin texture. (Used with parental permission for academic publication).

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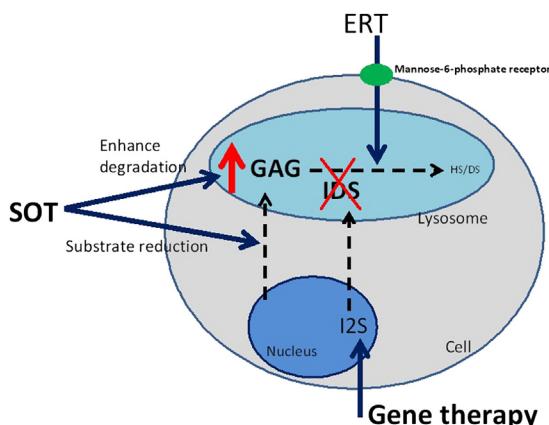


Fig. 2. Future perspectives for further treatment modalities for type 2 mucopolysaccharidosis. DS = dermatan sulphate; ERT = enzyme replacement therapy; GAG = glycosaminoglycans; HS = heparin sulphate; I2S = iduronate 2-sulfatase gene (\uparrow accumulation of GAG, \times = broken IDS); SOT = substrate optimization therapy.

and possible generation of harmful autoantibodies. The high cost of ERT is also an issue. Worldwide, there are around 720 known patients with type 2 MPS, 15% of which are now receiving ERT. The yearly cost for the enzyme is already around \$62 million. In Taiwan, there are now 16 patients with type 2 MPS and normal cognitive function who are receiving ERT; the annual cost for the enzyme is around \$9 million. Most importantly, ERT is not effective in central nervous system involvement.

For future perspectives, an effective way to deliver enzyme across the blood–brain barrier is crucial for clinical studies. Noninvasive gene targeting to the central nervous system is still in the early stage of development. Additionally, controlled clinical trials of hematopoietic stem cell transplantation, substrate

reduction therapy (such as miglustat), substrate optimization therapy, and selective inhibitors of GAG biosynthesis (Fig. 2), and more studies on a created IDS-knockout mouse model are needed. To identify individuals who might benefit from early treatment, a program of newborn screening for patients with type 2 MPS is now being developed.

ERT alone is not a cure for type 2 MPS; its long-term safety and efficacy also need to be determined through programs of the International Hunter Outcome Survey. Managing the burden of residual disease such as heart and skeletal complications should be addressed. A combination of different treatment modalities may contribute to a better treatment outcome in the future.

Further reading

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