Sanfilippo disease (mucopolysaccharidosis type III): Early diagnosis and treatment

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MUCOPOLYSACCHARIDOSIS TYPE III (SANFILIPPO SYNDROME): EMERGING TREATMENT STRATEGIES

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ABSTRACT

Mucopolysaccharosis III (MPS III) is a lysosomal storage disorder and belongs to the group of mucopolysaccharidoses. MPS III is caused by a deficiency of one of the four enzymes catalyzing the degradation of the glycosaminoglycan heparan sulfate. MPS III is clinically characterized by progressive dementia with distinct behavioral disturbances and relatively mild somatic disease. This review will summarize and discuss the available and potential future therapeutic options for patients with MPS III. This includes enzyme replacement therapy (ERT), hematopoietic stem cell transplantation (HSCT), substrate reduction therapy (SRT), chaperone-mediated therapy, and gene therapy. Although clinical efficacy has not yet been fully demonstrated for any of these therapies, it is likely that future developments will lead to disease-modifying treatment for this devastating disease.
INTRODUCTION

Mucopolysaccharidosis type III (MPS III, Sanfilippo syndrome) is one of the over 40 currently recognized lysosomal storage disorders (LSDs). MPS III is caused by an autosomal recessive inherited deficiency of one of the four enzymes involved in the lysosomal degradation of heparan sulfate, a glycosaminoglycan. Glycosaminoglycans (GAGs) are long unbranched polysaccharides and consist of repeating disaccharide units. All GAGs except hyaluronic acid contain sulfate groups at various positions. GAGs are covalently bound to proteins forming proteoglycans. These proteoglycans are abundant in the extracellular matrix while some proteoglycans are inserted in the plasma membrane or are contained in secretory granules. In addition, proteoglycans are involved in cellular homeostasis and cellular signaling pathways by binding to specific protein ligands. GAGs are constantly recycled by specific lysosomal degradation pathways. Heparan sulfate contains a glucuronic acid (GlcA) linked to N-acetylglucosamine (GlcNAc) as the most common disaccharide unit.

MPS III is caused by a deficiency of one of the four enzymes involved in the lysosomal degradation of heparan sulfate: heparan N-sulfatase (SGSH), α-N-acetylglucosaminidase (NAGLU), acetylCoAα-glucosaminideacyetyltransferase (HGSNAT) and N-acetylglucosamine-6-sulfatase (GNS). A deficient activity of one of these four enzymes causes the four MPS III disease subtypes A, B, C, or D, respectively.

All of the enzymes involved in the breakdown of heparan sulfate are acid hydrolases except HGSNAT, which is bound to the membrane of the lysosome. MPS III is the most frequently occurring type of the seven mucopolysaccharidoses (MPSs) with an estimated incidence of 0.28 - 4.1 per 100,000. MPS IIIA and B are the most common subtypes of MPS III, while the subtypes C and D are much rarer.

CLINICAL SIGNS AND SYMPTOMS

In contrast to many LSDs, patients with MPS III have only mild somatic symptoms. However, the central nervous system (CNS) is severe and progressively affected in MPS III. The clinical course of MPS III can generally be divided into three consecutive phases. The time course of the different phases may vary remarkably. After an initial symptom free interval, a developmental delay becomes apparent. This usually occurs at the age of one to four years. Slowing of speech development is often the first sign in MPS III. The second phase generally starts around the age of four and is characterized by often severe behavioral disturbances, characterized by incorrigible hyperactivity and temper tantrums, profound sleep disturbances and intellectual decline. In the final third phase of the disease, the behavioral problems slowly disappear with the onset of severe dementia and decline of all motor functions, eventually resulting in full loss of locomotion, dysphagia and pyramidal tract lesions. Death, often due to pneumonia, usually follows at the end of the second or beginning of the third decade of life. However, MPS III comprises a wide clinical spectrum of severity, and survival into the fourth decade has been reported.
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PATHOPHYSIOLOGY

For long, a relatively simple and straightforward pathophysiological mechanism was considered to cause the CNS disease in MPS III: accumulating heparan sulfate within the lysosomes of neuronal cells results in a perturbation of multiple cellular functions and thus in progressive CNS disease. Studies in animal models and, very limited, in humans, revealed however that changes in cellular homeostasis resulting from impaired degradation of GAGs are more complex and involve pathways not directly related to GAG metabolism. Negatively charged GAGs influence ligand-receptor interaction by stabilizing receptors at the cell surface and by direct binding and presentation of ligands to their respective receptor. Free GAGs within the extracellular matrix can also sequester humoral factors. Accumulating GAGs may thus affect the complex signaling pathways that occur between cells. Secondly, deficiency of one lysosomal hydrolase appears to lead to alterations of the enzyme activities of other lysosome hydrolases. Consistent observations in MPSs include increased activity of β-hexosaminidase, α-glucosaminidase, β-galactosidase, and β-gluronidase within the liver and brain with decreased activity of sialidase, and N-acetylgalcosaminyltransferase. The cause of the changed activity in other lysosomal enzymes is largely unknown, but has been postulated to reflect the increased cellular mass of lysosomes or the stabilization of enzymes by the storage material. Thirdly, accumulation of glycosphingolipids, most notably GM2 and GM3 gangliosides, has been observed and studied in various animal models with MPSs. Accumulation of GM2 and GM3 is remarkable, as the degradation of glycosphingolipids does not require the involvement of any of the hydrolases that are deficient in the MPSs. In addition to these gangliosides, studies of the goat model of MPS IIIID revealed significant elevations of the glycosphingolipid GD3 and lactosylceramide in the prenatal, neonatal and adult brain. Accumulating gangliosides, particularly GM2, are considered to induce changes in dendritic and axonal morphology. Increased concentrations of sphingolipids may be linked to the ability of GAGs to inhibit the activity of (other) hydrolases, in particular sialidase, as discussed above. Fourthly, recent studies in murine models of MPS I, MPS IIIA and MPS IIIB have shown accumulation of free unesterified cholesterol in the CNS. Cholesterol appears to accumulate only in neurons that also accumulate gangliosides, while in some neurons gangliosides accumulate without cholesterol. Accumulation of unesterified cholesterol again appears to be a response to ganglioside accumulation which in turn is secondary to GAG storage. Because gangliosides and cholesterol are part of the important signaling platforms in membranes known as rafts, their co-localization in individual neurons may reveal the presence of defects in the composition, trafficking and/or recycling of raft components, and therefore may represent possible new mechanisms to explain neuronal dysfunction in MPS. Fifthly, inflammatory responses have been implicated in the pathophysiology of CNS disease in several LSDs. Studies in murine models of MPS I and MPS IIIB revealed perineuronal microglial activation within the CNS and increased transcripts of several mediators in the macrophage/monocyte activation pathway. Evidence is also emerging for
the involvement of inflammation in the pathophysiology of bone and joint disease in those MPSs in which bones and joints are affected (MPS I, II, IV and VI)\textsuperscript{15,16}. The direct mediators of the inflammatory response in the CNS and skeletal tissues and the specific role GAGs may play in this process remain largely unknown. However GAGs display both pro-inflammatory and anti-inflammatory properties \textit{in vitro} and have been implicated in the pathogenesis of rheumatoid arthritis and osteoarthritis, and other autoimmune inflammatory diseases \textsuperscript{17}. Finally, in MPS I levels of the heparin cofactor II thrombin complex (HCII-T) are elevated. HCII is a member of the serpin family, with thrombin as its main target protease \textsuperscript{18,19}. Interestingly, many members of the serpin family, including glial-derived protease nexin (PN-1), are known to be preferentially activated by GAGs \textsuperscript{20}. Serine proteases and their inhibitors play an important role in the CNS. A disturbed balance between proteolytic activity and protease inhibition might contribute to the development of neurodegeneration.

Clinical management of patients with MPS III currently still consists mainly of supportive care, aimed at ameliorating symptoms and prevention of complications. Behavioral problems are, for example, a predominant symptom in MPS III patients. Treatment with risperidone has been shown to be effective for behavioral problems \textsuperscript{21}. In addition, sleep disturbances are common, severe, and often difficult to manage \textsuperscript{3}. Melatonin in high dose was demonstrated to be most efficacious treatment \textsuperscript{22,23}. Benzodiazepines may also help to ameliorate the sleeping problems.

Fortunately, several new disease-modifying therapies are currently being developed and studied. In the next sections we will review the current status of studies, and discuss their potentials.

**ENZYME REPLACEMENT THERAPY**

Enzyme replacement therapy (ERT) is currently the most successful therapy for the treatment of the non-neurological signs and symptoms of several LSDs \textsuperscript{24}. ERT, using enzymes produced by genetic engineering, has been approved for MPS I, II and VI, Gaucher disease, Fabry disease and Pompe disease \textsuperscript{25}. The pharmacological principle of ERT is based on the concept that recombinant lysosomal hydrolases are internalized by cells and tissues through the mannose or mannose-6-phosphate receptor (MPR) pathways to be ultimately delivered to lysosomes where they are activated and replace the function of the defective hydrolases \textsuperscript{24}.

Although in animal studies some effect of high-dosed intravenous non-modified enzyme was detected on CNS storage material \textsuperscript{26-28}, intravenously administered enzyme cannot cross the blood-brain barrier (BBB), at least not in sufficient quantities, and therefore cannot prevent the progression of the neurological symptoms in LSDs with CNS involvement, such as MPS III.

Several promising approaches to achieve passage of an enzyme across the BBB are currently under investigation. The first option is to fuse the therapeutic enzyme with a protein for which a receptor is expressed on the surface of cerebral vascular endothelial
cells, thereby using the option of receptor mediated protein transport \(^{29,29,30}\). In fibroblasts of MPS I patients the fusion of the amino terminus of α-L-iduronidase, the missing enzyme in this disease, to the carboxyl terminus of the CH3 region of the heavy chain of the chimeric monoclonal antibody to the human insulin receptor resulted in a decline of GAG accumulation with 70\% \(^{31}\). The fused protein acts as a molecular “Trojan Horse” potentially ferrying α-L-iduronidase into the brain, and 1\% of the intravenously injected dose was indeed demonstrated to be present in primate brain after intravenous injection \(^{31,32}\). Another option, making use of nanotechnology \(^{33}\) relies on the adsorptive mediated transport across the blood-brain barrier \(^{29,30}\). Engineered nanoparticles, either polymeric or liposomes, have a relatively large surface enabling binding, absorption and carrying of drugs and proteins \(^{34}\). Penetration of the brain by nanoparticles may be achieved by paracellular movement following disruption of endothelial tight cell junctions, simple passive diffusion, transport or endocytosis \(^{35,36}\). Several studies have demonstrated that nanoparticles might indeed be used for CNS targeted drug and gene delivery \(^{37-40}\). Although this appears a promising technique, thus far, no studies have been published using nanotechnology in animal models of MPS III or other LSDs.

A completely other approach for overcoming the BBB is by injection of the enzyme directly into the brain or into the cerebrospinal fluid (CSF) \(^{41}\). Experiments in animal models of MPSs, including MPS IIIA, showed that the recombinant enzyme injected in the intrathecal space, is distributed throughout the central nervous system and can penetrate brain tissue where it promotes clearance of lysosomal storage material \(^{42,43}\). This approach could delay neurodegenerative changes in younger MPS IIIA mice \(^{41}\), and frequent administration of the enzyme seemed to improve behavior in these mice \(^{42}\). Intracisternal enzyme delivery in three MPS IIIA dogs resulted in a widespread enzyme delivery in the superficial and deep brain and reductions in storage of a heparan sulfate derived disaccharide \(^{44}\). No neurobehavioral analysis was conducted in this study.

Currently, first clinical trials using intrathecal enzyme therapy are conducted in MPS I and II. Based on the preclinical data for MPS IIIA, intrathecal enzyme delivery is also a promising option for halting progressive neurodegeneration in MPS III and the first clinical studies in MPS IIIA will probably follow shortly.

### STEM CELL TRANSPLANTATION

Hematopoietic stem cell transplantation (HSCT) as a potential therapy for CNS disease in LSDs was first reported by Hobbs and co-workers in 1981 for the severe neurological phenotype of MPS I (Hurler phenotype) \(^{45}\). Since then, over 400 patients with MPS I, Hurler phenotype, have been transplanted \(^{46}\). HSCT aims at introducing donor stem cells with normal enzyme activity in the patient. The various peripheral tissues (including the liver, spleen, lungs, and heart) presumably benefit from both enzyme secretion by infiltrated (donor) macrophages as well as enzymes secreted into the bloodstream by (donor) leukocytes. The CNS relies on infiltration by donor macrophages, which may
differentiate into microglia cells in the CNS, secreting the deficient enzyme for recapture by the surrounding neurons 47. Donor-derived macrophages and microglia thus become a stable source of endogenous enzyme cross-correcting defective cells.

HSCT was also performed in patients with MPS IIIA and MPS IIIB 48-50. However, no clear benefit was observed. As these transplantations were usually performed after the onset of neurological disease, the outcome is difficult to interpret 51. Bone marrow transplantation in an early diagnosed patient with MPS IIIA and an untreated sibling, however, also showed no preservation of neurocognitive functioning 49. Therefore HSCT using bone marrow derived stem cells is currently not considered as a treatment option in MPS III 50,52. Human umbilical cord blood (hUBC) is considered as an excellent source for hematopoietic stem cells, especially in the absence of a HLA identical sibling. In addition, hUCB contains more hematopoietic stem progenitor cells that appear to have an unusual capacity to develop in non-blood cells such as neural cells 53. Administration of umbilical cord blood derived stem cells into the lateral ventricle or intravenous administration of these stem cells in mice with MPS IIIB improved the cognitive outcome 54,55. Transplantation of hUCG derived stem cells has recently been used to transplant several children with MPS IIIA or MPS IIIB. However, it is yet unclear whether this approach results in protection of the CNS from degeneration in MPS III patients.

CHEMICAL CHAPERONES

Lysosomal enzymes are synthesized and secreted into the endoplasmic reticulum (ER) in a largely unfolded state. An efficient intracellular system controls that only properly folded proteins are transported to the Golgi apparatus for further maturation. Misfolded enzymes are rapidly degraded by proteasomes. Specific molecules, called “chaperones” are able to increase residual enzyme activity by rescuing misfolded mutant proteins from rapid endoplasmic reticulum-associated degradation (ERAD), and promoting the processing and trafficking of mutant enzymes to the lysosomes. As a result, the enzyme is still able to fulfill its function, despite of the initial misfolding caused by a missense mutation 56,57. Chaperone mediated therapy might be an efficient therapeutic approach for several LSDs. As it is generally assumed that a threshold activity of approximately 10% is sufficient to prevent storage in LSDs 58, even a minor increase in enzyme activity due to the effect of a chaperone is likely to have an impact on disease pathology and to be beneficial for patients 59. An important advantage of chaperones is that they are small and can cross the BBB. Chaperones therefore have potentials for the treatment of MPS III. Molecules that have been studied for potential functions as chaperones in MPS IIIB are 2-acetamido-1,2-dideoxynojirimycin (2AcDNJ) and 6-acetamido-6-deoxycastanospermine (6AcCAS). These molecules may inhibit the involved enzyme NAGLU at high concentrations but act as chaperones in lower concentrations 60,61. By using the same approach one specific missense mutation in MPS IIIC could be partially rescued in fibroblasts by using low concentrations of the competitive inhibitor of HGSNAT 62.
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SUBSTRATE REDUCTION THERAPY

Substrate reduction therapy (SRT), also named substrate deprivation therapy (SDT), in MPS III aims at reducing the synthesis of GAGs, and thereby reducing the amount of accumulating heparan sulfate. Molecules used to inhibit GAG synthesis in the setting of SRT are relatively small and may well be able to cross the BBB. Inhibitors of GAG synthesis include agents that block the synthesis of common intermediates, e.g. deoxygenated and fluorinated analogs of N-acetylgalactosamine. Other compounds such as diethylcarbamazine, monensin, and brefeldin A, alter GAGs synthesis, including heparan sulfate, by disrupting the organization of the endoplasmatic reticulum and Golgi apparatus. However, no studies in MPS III models using these compounds have yet been published.

Genistein is an isoflavone, a major class of flavonoids mainly present in soy-bean and soy-based foods. Genistein inhibits GAG synthesis, including heparin sulfate and dermatan sulfate via the epidermal growth factor (EGF)-dependent pathway. This pathway is involved in the regulation expression of genes involved in the biosynthesis of GAGs. Genistein has been shown to significantly inhibit GAG synthesis in cultured skin fibroblasts of MPS patients, resulting in a significant reduction in GAG accumulation, including heparan sulfate. A recent study revealed that four natural isoflavones close to genistein may be even more efficient than genistein in reducing GAG accumulation in MPS III A and MPS VII fibroblasts. These results, however, cannot easily be compared with a previous study by Piotrowska et al. as different methods for GAG quantification were used, assessing total GAG level in MPS fibroblasts rather than GAG synthesis rate.

In another study, a combination of three isoflavones appeared even more efficient than one isoflavone alone, suggesting a synergistic effect of these molecules. Finally, several studies revealed a strong anti-inflammatory effect of isoflavones. This effect might be valuable in the treatment of MPS III patients, as neuroinflammation has been proposed to be involved in MPS III. Treatment with genistein for eight weeks of MPS III B mice resulted in a clear reduction in liver lysosome compartment size in both male and female MPS III B animals. In this study, a significant dose-dependent reduction of total liver GAGs and hair morphology in male MPS III B mice was also observed. No change in total GAGs, lysosomal size or reactive astrogliosis in the brain cortex was observed, which could possibly be due to the relatively short treatment period. However, in mice with MPS II decreased GAG-deposits were found around the choroid plexus by histochemistry in both groups treated with genistein different doses of genistein.

In an open label pilot study in 10 children with Sanfilippo disease types A and B specific effects could be demonstrated after 12 months of oral treatment with a genistein-rich isoflavone extract. Treated patients showed a decrease in urinary GAG levels and improvement in hair morphology, cognitive functions and behavior. These promising results in combination with easy availability as ‘neutriceutical’, has resulted in a wide spread use of genistein in MPS III patients in many countries. Recently, a double blind placebo controlled cross-over study on the efficacy of genistein in MPS III was started (www.trialregister.nl, identifier NTR1826). Thirty patients are included in this study. First results are expected at the end of 2010.
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GENE THERAPY

MPS III is a candidate for therapy by gene transfer, since it is a single gene disorder and not subject to complex regulation mechanisms. In addition, the size of the cDNA coding for most lysosomal enzymes allows the use of vector systems with limited carrying capacity, such as adeno-associated virus (AAV).

Ex vivo gene therapy

Ex vivo gene therapy refers to removal of cells, such as hematopoietic stem cells (HSC), genetic modification in vitro, followed by reinfusion of the modified cells. The use of autologous cells prevents graft-versus-host disease and does not require the availability of a HLA compatible donor. HSC-directed gene therapy was able to partially reduce the manifestations of CNS pathology in MPS IIIB mice, which was attributed to migration of cells into the brain. A recently published successful trial on ex vivo gene therapy in X-linked adrenoleukodystrophy, an inborn error of peroxisomal metabolism, has renewed the expectations of this approach after previous studies did reveal potential side effects. However, the disappointing results of HSCT in MPS III patients suggest that ex vivo gene therapy using HSC might fail to correct the CNS disease in patients with MPS III.

In vivo gene therapy

Different strategies for in vivo gene therapy have been studied in MPS III. In order to overcome the BBB, the recombinant adeno-associated virus (AAV) vector was injected directly into the CNS in MPS III mice resulting in improvement of CNS pathology and/or improvement of behavioral. In MPS IIIB mice direct injection of a lentiviral NAGLU vector into the CNS was used to deliver the functional human NAGLU gene into the brain. This resulted in a restoration of enzyme activity with a sustained expression throughout a large portion of the brain, and a significantly improvement of behavioral performance in the treated animals at six months. Moreover, the study of Fraldi et al. demonstrated that co-delivery of sulfatase-modifying factor 1 (SUMF1) enhances the efficacy of gene therapy by AAV-mediated delivery of the sulfamidase gene intraventricular in MPS IIIA mice. There was an increase of SGSH activity, reduction of lysosomal storage and inflammatory markers in several brain regions. Also, the MPS IIIA mice displayed an improvement in both motor and cognitive functions. However, extensive toxicology and safety studies need to be done before in vivo gene therapy for CNS disease in MPS III can be studied in man.

TIMING OF TREATMENT

The first clinical sign in almost all patients with MPS III is developmental delay. As the optimal outcome of all emerging disease-modifying therapies in MPS III is stagnation of the otherwise invariably progressive decline of cognitive functions, early initiation of therapy, at least before extensive and irreversible damage to the CNS has occurred, is essential. Early diagnosis of MPS III is paramount and currently depends on the recognition of the pattern of the first clinical signs and symptoms, being slowing of development, especially...
of speech, in combination with behavioral disturbances. As these signs and symptoms are non-specific, a long interval before diagnosis is established is common. Campaigns to increase awareness of MPS III in the medical community may lead to earlier diagnosis. However, the best strategy would be to start therapy in the presymptomatic period, which generally is in the first one to two years of life. Identification of patients during this period can only be achieved by screening of patients at risk (e.g. sibs) or by population (newborn) screening. Newborn screening by measuring enzyme activity in dried blood spots has recently been developed for a number of LSDs (including Pompe disease, Fabry disease and MPS II) \(^{91-93}\), and the pilot studies on the efficacy of screening have been published \(^{94,95}\). If disease modifying treatment strategies have been developed for MPS III and tested, studies on potential approaches for newborn screening need to follow immediately.

**BIOMARKERS**

Newly developed, invasive and often costly therapies for LSDs, including MPS III, call for research on suitable biomarkers to monitor onset and progression of disease, as well as the efficacy of the therapeutic intervention. Recent studies revealed potential biomarkers as MIP-1 \(\alpha\), and HCII-T for MPS III \(^{96,97}\). MIP-1 \(\alpha\) is an inflammatory chemokine playing a role in macrophage recruitment, inducing monocytes to infiltrate the CNS. HCII-T is also a biomarker, and its complex formation is mainly activated by GAGs. However, the value of these biomarkers in establishing efficacy of therapy in MPS III still needs to be studied.

**DISCUSSION**

The development of disease modifying therapy for MPS III poses enormous challenges. This is mainly due to the fact that the devastating clinical symptoms in MPS III result from progressive CNS disease and because the pathophysiological mechanisms of the neurodegenerative processes are still not well understood. Nevertheless, an impressive number of *in vitro* and animal studies investigating potential therapeutic approaches in MPS III have been performed in recent years. Only a few of these studies have already resulted in studies involving human patients.

The BBB effectively blocks the transfer of intravenously supplied enzymes, and several studies focus on pharmacological mechanisms enabling the transport of recombinant enzyme across the BBB. One approach to circumvent the BBB is direct injection of the enzyme into the CNS compartment and experiments in the mouse and dog model of MPS III indeed demonstrated a decrease in CNS pathology and improvement in learning in the mice. This will probably result in a phase I/II trial on intrathecal delivery of recombinant enzyme in patients with MPS IIIA.

The option of HSCT, which is an effective treatment of the CNS diseases in the severe phenotype of MPS I, needs to be further explored for MPS III. Although previous studies suggested that transplanted hematopoietic stem cells, at least those derived from bone marrow, are not able to halt the progression of dementia in MPS III, the use of an alternative
stem cell source (hUCB) might be more efficacious. hUCB derived HSCT has indeed been performed in a number of MPS III patients and it will prove essential to closely monitor disease progression in those patients in order to be able to study its clinical efficacy.

Another approach try to halt the neurological decline in MPS III patients is by inhibiting the synthesis of heparan sulfate, the primary accumulating GAG in MPS III. *In vitro* studies using isoflavones such as genistein, derived from soy beans, revealed that they can inhibit GAG synthesis in MPS III fibroblasts and the results of a first, open label, clinical trial are very encouraging. A placebo controlled double blinded trial on the efficacy of genistein in patients with MPS III is currently conducted.

In addition to these first studies and trials in patients, a number of other treatment strategies including other approaches to inhibit synthesis of heparan sulfate as well as gene therapy will probably enter clinical studies within the next years. It may well be that different therapeutic strategies will prove to be effective for different types of the disease, e.g. because the enzyme acetyl CoA α-glucosaminide acetyltransferase, which is deficient in MPS IIIC, is a transmembrane protein and not an intralysosomal hydrolase. In addition, different treatment strategies may prove to be the most efficacious for different phenotypes. For example, SRT might be most effective in the more attenuated forms of MPS III. In addition, combination of different therapeutic strategies, e.g. intrathecal ERT in combination with SRT, may prove to be an effective approach.

Finally, whatever (combination of) therapeutic strategies will prove to be the most successful, early start of therapy, preferably before the onset of CNS disease and thus during the presymptomatic stage of the disease, will be essential. As this can only be achieved by newborn screening for MPS III, future studies should be directed to investigate the feasibility of screening for MPS III in dried blood spots.
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