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A Meta-Analysis of Clinical Advancement in Sanfilippo Syndrome Type A

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Abstract

Sanfilippo syndrome (also known as MPS III) type A is caused by the mutation of gene SGSH on chromosome 17, region 17q25.3. Sanfilippo syndrome is a recessive gene affecting 1 in 70,000 babies each year. This mutation affects the mucopolysaccharides and causes the patient to lose an enzyme that is crucial to breaking down the mucopolysaccharide heparan sulfate. Heparan sulfate is stored in the cells instead of being broken down, causing progressive damage. Symptoms become apparent after the age of 1-year-old and learning abilities decline between the ages of 2 and 6. The symptoms and progression rate are different in each patient. Eventually, physical growth slows, resulting in small stature. Some other common symptoms include behavioral problems, coarse facial features, full lips, heavy eyebrows, sleep difficulties, stiff joints, and difficulty walking. There is no known cure and no approved treatment for MPS III. Bone marrow transplants and enzyme replacement therapy have not been effective in treating MPS III. Currently, gene therapy, chaperone therapy, and intrathecal enzyme therapy are being explored as treatments for Sanfilippo syndrome.

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INTRODUCTION

Background information about the disease

Sanfilippo syndrome (also known as MPSIII) type A is caused by the mutation of the gene encoding SGSH, N-sulfoglucosamine sulfohydrolase, on chromosome 17, region 17q25.3

- It is a recessive gene that affects around 1 in 70,000 babies each year
- This mutation affects the mucopolysaccharides and causes the patient to lose an enzyme that is crucial to breaking down heparan sulfate
  - Heparan sulfate is stored in the cells instead of breaking down and causes progressive damage
- Symptoms become apparent after the age of 1-years-old
  - Learning abilities decline after the ages of 2 and 6
  - The symptoms and progression rate are different in each patient
  - Limit of physical growth, resulting in small stature
  - Other common symptoms include:
    - Behavioral problems
    - Coarse facial features
    - Full lips
    - Heavy brows
    - Sleep difficulties
    - Stiff joints
    - Difficulting walking
- Diagnosis includes a urine test looking for high levels of mucopolysaccharides

Child with MPS III syndrome. Image taken from National MPS society

PROSPECTIVE TREATMENT

Enzyme Replacement Therapy and Outcomes

Enzyme replacement therapy has gone through multiple trials to see if testing different ways to replace the missing enzyme that inhibits the degradation of MPS.

- Animal models of enzyme therapy
  - Protein fusion and direct administration to CNS have been proven effective
  - Problems are a high concentration of enzymes are needed and fusion to CNS is highly invasive and may not work on children, the main affected population
- Clinical enzyme replacement trials
  - Began in 2016 with 12 patients
  - In the trial recombinant human heparan-N-Sulfatase has been administered intrathecally to each of the patients monthly
  - 4 showed a decline in development 6 remained stable and 2 were inconclusive

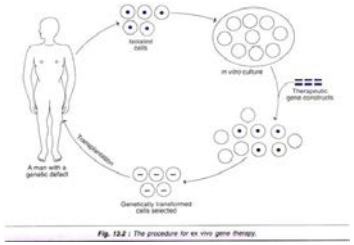

Fig. 13.2 : The procedure for ex vivo gene therapy.

Ex Vivo gene therapy applied to bone marrow tissue.

Gene therapy in Sanfilippo Syndrome Type A is used in hopes that the stem cells that are introduced from the bone marrow of a healthy individual will be catalytically active and this activity will spread to native cells so that they will be catalytically active too.

- Preliminary testing in mice showed significant decrease in activity after treatment if treated early. Mice treated with a Sulfate Modifying Factor 1 in the SGSH gene using an internal ribosomal entry site (SGSH-IRES-SUMF1) showed activity similar to normal mice. Early treatment by injection was sufficient in prevention or delay of central nervous system issues in mice with Sanfilippo Syndrome. This study and others like it allowed human clinical trials to begin. (Fraldi A, et al.)
- In human trials, a similar result was found. The best outcomes are from younger patients who received treatment early. During the trials, patients showed no negative side effects at the injection site. (Tardieu M,et al.)

Treatment for this disease using stem cells in bone marrow is still in trials but looks hopeful.

Table 1

Summary of studies conducted on development of therapies for Sanfilippo disease (MPS III) and reported during last 3 years (2014–2017)

MPS III subtype	Models or trials	Therapies investigated in recent years			
		ERT	SRT	Other small molecules	Gene therapy
MPS IIIA	Cellular models	X	X		
	Animal models	X			X
	Clinical trials	X	X		X
MPS IIIB	Cellular models	X	X	X	
	Animal models	X	X		X
	Clinical trials		X		X
MPS IIIC	Cellular models		X	X	
	Animal models				
	Clinical trials		X		
MPS IIID	Cellular models				
	Animal models				X
	Clinical trials				

The availability of reports on particular kinds of therapies and models are marked by X

Abbreviations: MPS mucopolysaccharidosis, ERT enzyme replacement therapy, SRT substrate reduction therapy

Lidia Gaffke Summary of studies conducted on development of therapies for Sanfilippo disease (MPS III) and reported during last 3 years (2014–2017)

CONCLUSION

Overall, treatments for Sanfilippo Syndrome type A are still in the preliminary stages. Enzyme replacement therapy and gene therapy currently are at the forefront of research. The advancement of clinical trials to human subjects will be of principal interest as research continues. MPS III is a syndrome associated with high lethality: it is crucial that therapies are effective for young individuals. Due to this, **our meta-analysis found gene therapy to be a more promising avenue of treatment**. Future research should heavily invest in gene therapy to improve outcomes for affected individuals.

Psychological and Cultural Considerations

Psychological Symptom Management:

Sanfilippo syndrome presents initially with psychosomatic symptoms, similar to those seen in individuals with ADHD. Research into management of these symptoms is critical to patient wellbeing as well as elevating quality of life.

Cultural Considerations:

Attention to areas of prevalence should also be taken into account with this syndrome. Geographic distribution of Sanfilippo shows the highest density of cases in Australia. Distribution data outside of Europe and Australia is lacking. It is highly possible that cases are under reported in developing countries.

Citations

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- Gaffke, Lidia et al. "How close are we to therapies for Sanfilippo disease?." Metabolic brain disease vol. 33,1 (2018): 1-10. doi:10.1007/s11011-017-0111-4
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