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MPS Research Highlights at WORLD*Symposium* 2020

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Mucopolysaccharidoses

- A group of lysosomal storage disorders
- Genetic disorders in which mutations in different genes leads to abnormal accumulation of complex carbohydrates
  - Mucopolysaccharies or glycosaminoglycans
- Numerous MPSs and each MPS may also have numerous subtypes
- Often have striking skeletal features. May or may not have behavioral/cognitive difficulties

NIH Rare Disease Database: MPS. 2019. https://rarediseases.info.nih.gov/diseases/7065/mucopolysaccharidosis

Mucopolysaccharidoses

MPS Type	Common Name	Gene Mutation	Treatment
MPS I	Hurler syndrome	*IDUA*	HSCT, ERT, symptomatic/supportive
MPS II	Hunter syndrome	*IDS*	ERT, symptomatic/supportive
MPS III	Sanfilippo syndrome	*GNS, HGSNAT, NAGLU, SGSH*	Symptomatic/supportive
MPS IV	Morquio syndrome	*GALNS, GLB1*	ERT, symptomatic/supportive
MPS VI	Maroteaux-Lamy syndrome	*ARSB*	ERT, symptomatic/supportive
MPS VII	Sly syndrome	*GUSB*	ERT, symptomatic/supportive

NIH Rare Disease Database: MPS. 2019. https://rarediseases.info.nih.gov/diseases/7065/mucopolysaccharidosis

WORLD*Symposium*

- Annual conference focused on lysosomal storage disorders
  - MPSs, Fabry disease, Gaucher disease, etc
- 4 day event every February
  - Day 1 & 2 – Basic research
  - Day 2 & 3 – Translational research
  - Day 3 & 4 – Clinical research
- 446 poster presentation
- 84 oral presentations

MPS and Reproduction

- Peter, Cagle; Atlanta, GA
- Can women with MPS have normal menstruation and pregnancy?
  - Case-control study with 33 MPS women [MPS I (10), MPS IV (17), MPS VI (5), and MPS VII (1)]
  - Menstrual questionnaire
    - MPS women scored abnormally higher but difference not statistically significant
  - Pregnancy
    - 6 women with MPS had successful pregnancy.
      - Complications included spotting, gestational diabetes, prolonged labor, and excessive blood loss

Peter, Cagle. *Mol Gen Metab.* 2020; 129: S127-A128.

MPS and Life Challenges

- Thomas, Morrison; Amersham, UK
- MPS Society survey about living with MPS
  - 27 adults with MPS I (30%), MPS II (15%), MPS IV (48%), MPS VI (7%)

Most Common Challenges	What Patients Would Like Help With
• Loss of mobility/unable to perform daily tasks (37%) • Coming to terms with their condition (19%) • Unable to find a job (15%) • Loss of cognitive ability (7%)	• Funding support to manage health and housing (19%) • Finding MPS medical specialists (11%) • Information about adult services (7%) • Improving psychological care (7%)

Thomas, Morrison. *Mol Gen Metab.* 2020; 129: S151.

MPS: Comorbidities

- Del Toro et al; Barcelona, Spain
- Hydrocephalus observed in some MPS patients
  - Can be difficult to diagnose
  - 12 patients with MPS
    - 10 with MPS II
    - 1 with MPS VI
    - 1 with MPS VII
  - Authors speculate hydrocephalus underdiagnosed in MPS patients

Del Toro et al. *Mol Gen Metab.* 2020; 129: S47.

MPS I Highlights at *WORLDSymposium*

- Bloomfield A et al; Manchester, UK
- Long-term ambulatory outcomes in Hurler syndrome patients after HSCT
- Question – does HSCT improve ambulation as well as it improves neurologic symptoms?
- 15 adults with Hunter syndrome who received HSCT as children

Ambulatory Abilities	Interventions

• 10 regularly used wheelchair
• 9 able to perform a 6MWT (median 354.3 m)
• 6 unable to do a 6MWT
  • 3 could do a 10 meter walk test
  • 2 could walk 5 meters
	• 8-plate insertions (n=7)
	• Spinal fusion (n=4)
	• Hip surgery (n=5)
	• Tibial osteotomies (n=2)

Bloomfield et al. *Mol Gen Metab.* 2020; 129: S34 –S35.

MPS I Highlights at *WORLDSymposium*

- Burlina A et al; Padova, Italy
- Case study examined use of newborn screening to diagnose MPS I early and begin treatment
- Between 2015 – 2019, 127,869 babies screened and 2 babies identified
- MPS I diagnosis confirmed and both babies started ERT within 15 days of birth
- Mutations found:
  - homozygous for the mutation p.P533R (Hurler to Hurler/Scheie phenotypes)
  - heterozygous for two severe mutations (c.46_57del12/p.Y201X). This baby also received HSCT at 6 months of age
- At present, both patients, now aged 2.5 years and 1.4 years, show no clinical signs of MPS I

Burlina et al. *Mol Gen Metab.* 2020; 129: S35 –S36.

MPS II Highlights at *WORLDSymposium*

- **Hunter syndrome**
- Esteban-Giner M et al; Alcoy, Spain
  - ERT review
  - 42 patient records examined
  - Records showed
    - Reduced GAG in urine
    - Decreased liver and spleen size
    - Increased 6MWT
    - Increased forced vital capacity
    - Reduced left ventricular mass index
    - Reduced mortality
  - Authors concluded ERT is effective in the treatment of MPS II

Esteban-Giner et al. *Mol Gen Metab.* 2020; 129: S54.

MPS II Highlights at *WORLDSymposium*

- Okuyama T et al; Tokyo, Japan
- JR-141 is an anti-transferrin receptor antibody fusion IDS that can cross the BBB
  - A 52-week, phase III study underway (N=28)
  - Preliminary 26 week data presented at the conference
  - Published results to date are vague but do indicate
    - HS concentrations in CSF decreased at week 26
    - Cognitive function and adaptive behavior remains stable (or improved)
    - Mild to moderate infusion-associated reactions reported
    - No serious side effects
  - Authors concluded that intravenous administration of 2 mg/kg/week JR-141 well tolerated and effective in treating CNS and systemic symptoms
- Escolar M et al; Pittsburg, PA
  - Late-breaking abstract (not published) showing interim results of RGX-121 gene therapy

Okuyama et al. *Mol Gen Metab.* 2020; 129: S119. Esteban-Giner et al. *Mol Gen Metab.* 2020; 129: S54.

MPS III Highlights at *WORLDSymposium*

Sanfilippo syndrome type IIIA

- Two gene therapies in clinical development
- Wijburg F et al; Amsterdam, Netherlands
  - AAV serotype rh.10 carrying the human SGSH
  - Phase 2/3, single-arm study
  - Up to 20 patients expected to be enrolled by mid 2020
  - Preliminary data presented at the conference
- Flanigan KM et al; Columbus, OH
  - ABO-102, a AAV9-based vector carrying human SGSH
  - 14 patients enrolled across 3 doses in a Phase 1/2 study
  - Preliminary data show a sustained, dose-dependent reduction in CSF HS levels
  - Higher dosed patients showed normal range of cognitive function

Wijburg et al. *Mol Gen Metab.* 2020; 129: S162. Flanigan et al. *Mol Gen Metab.* 2020; 129: S56 –S57.

MPS III Highlights at *WORLDSymposium*

Sanfilippo syndrome type IIIB

- One gene therapy in clinical development
- McBride KM et al; Columbus, OH
  - ABO-101, an AAV9-based vector carrying human NAGLU
  - 6 patients enrolled across 2 doses
  - Preliminary data show a sustained, reduction in CSF HS levels (N=3) and reduction in liver volume excess
  - Good safety profile observed

McBride et al. *Mol Gen Metab.* 2020; 129: S107.

MPS IV Highlights at *WORLDSymposium*

Morquio syndrome

- MARS (Morquio A Registry Study): Long term efficacy and safety with ERT
- Mitchell J et al; Montreal, Canada. Burton B, et al; Chicago, IL
  - 325 in the registry; 262 taking ERT [cohort 1 (clinical trial participants): n=119; mean ERT duration 6.37 yrs. Cohort 2 (independent participants): n=143; 2.77 years)
  - Efficacy and Safety

Parameter	Cohort 1	Cohort 2
6MWT	+16.7%	+45.8%
FEVI	+20.9%	+18.3%
FVC	+28.3%	+10.0%
Urine KS	-49.4%	-44.3%

Common AEs	Common SAEs
Musculoskeletal (6.1%)	Cerv cord compression (1.9%)
Infections/infestations (5.7%)	Knee deformity (1.9%)
Admin site rx (5.3%)	Hip dysplasia (1.1%)
Nervous system disorder (5.0%)	

Mitchell et al. *Mol Gen Metab.* 2020; 129: S95.

MPS VII Highlights at *WORLDSymposium*

Sly syndrome

- Two long term ERT studies reported
- Lau H et al; New York, NY
- Study in children <5 years of age (N=8 treated with ERT (vestronidase alfa). 7 completed a 48-week study and continued for up to 2.6 years)
  - Efficacy and Safety

Parameter	Change
Urine GAG	-61%
Height	+
Growth velocity	+
Hepatomegaly resolved	8 of 9 subjects
Splenomegaly resolved	3 of 5 subjects

Safety
Infections/infestations (50%)
Developed anti-drug antibodies (100%)
Discontinuation (0%)

Lau et al. *Mol Gen Metab.* 2020; 129: S112. Burton et al. *Mol Gen Metab.* 2020; 129: S36.

MPS VII Highlights at *WORLDSymposium*

Sly syndrome

- Wang R et al; Orange, CA
- Study in patients ages 8-25 years of age (N=12) treated with ERT (vestronidase alfa). All completed a 24-48 week study and continued for up to 144 weeks in an open label extension
- Results
  - Sustained uGAG reduction
  - Positive multi-domain response (pulmonary function, motor function, range of motion, mobility, visual acuity)
  - Reduced fatigue
  - Most adverse events mild to moderate. No treatment discontinuation due to AEs

Wang et al. *Mol Gen Metab.* 2020; 129: S158 – S159..

Summary

- MPSs are a group of lysosomal storage diseases
- Each MPS has its unique challenges and clinical outcomes that the care team needs to understand
- Current treatment options are effective
- Treatments in development showing additional promise