A Comparison of Developmental Trajectories in Sibling Cases with Neuropathic MPS-II Receiving Conventional and Novel Enzyme Replacement Therapies

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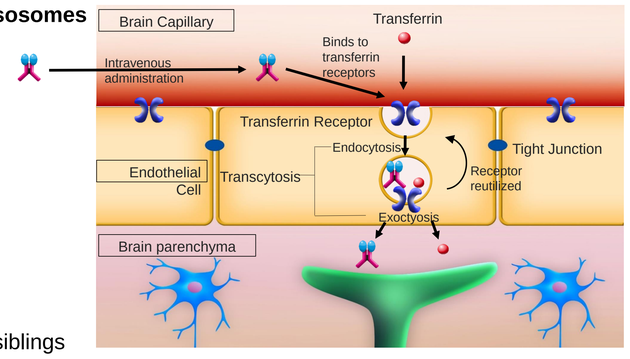
Introduction

Overview of MPS II and JR-141 (pabinafusp alpha)

- **An X-linked recessive lysosomal storage disease**
  - Mutations in the iduronate-2-sulfatase (IDS) gene
- **Pathological accumulation of glycosaminoglycans in the lysosomes**
  - A broad spectrum of symptoms, including CNS symptoms
- **Current ERT: ineffective for the CNS symptoms**
  - The enzyme cannot cross the blood-brain barrier (BBB)
- **JR-141: anti-human transferrin receptor antibody fused IDS**
  - Expected to cross the BBB
- **Phase II/III study**
  - Marked reduction in substrate accumulation in the CSF over 52 weeks administration of JR-141 (Okuyama *et al*., 2020)

Drug delivery through the Blood-Brain Barrier by transcytosis via transferrin receptors



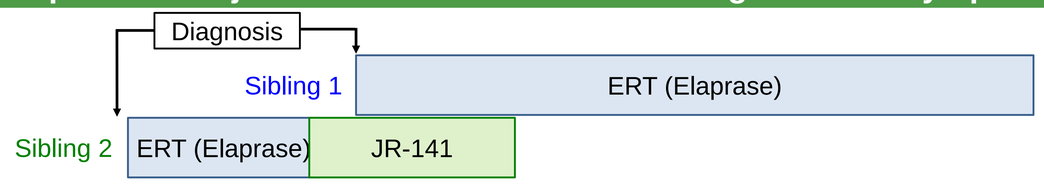
Objective:

- In this poster, we report the neurocognitive development in two siblings with MPS II harboring the same genetic mutation

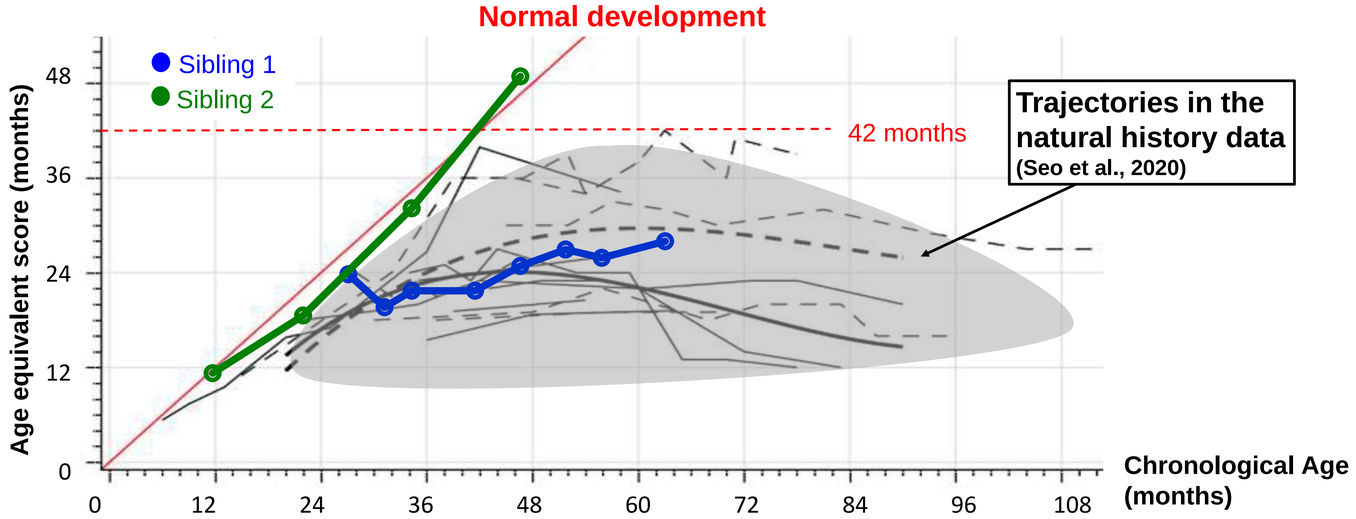
Patients' Background

	Sibling 1	Sibling 2
Genetic mutation	IDS c.419 G>T, p.G140V GGG(Gly)→GTV(Val)	
Diagnosis of MPS-II	Made at the age of 2yr 4m	Made prenatally
Conventional ERT with Elaprase	Initiated from 2yr 4m of age until now (9 yr)	Initiated from 1m of age, continued until 1yr 11m , then switched to JR-141
Treatment with JR-141	N/A	Initiated from 1yr 11m until now (4yr)
Past history	Inguinal hernia Hydrocele testis Mixed hearing loss Adenoid vegetation Chronic sinusitis Sleep apnea	Inguinal hernia Exudative otitis media Adenoid vegetation

Developmental Trajectories and Time-course Changes MPS II Symptoms of the Siblings



Normal development



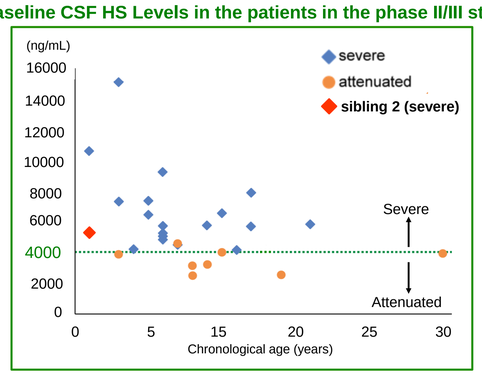
Hepatomegaly	Sib1			++		+					
	Sib2			-		-					
Skeletal deformity	Sib1			+							
	Sib2			-		-					
joint stiffness	Sib1			+				+			
	Sib2			-		-					

Age	Sibling 1	Sibling 2
10m		• Walks alone
1yr		• Utterance of one-word sentence
1yr 8m	• Walks alone	
2yr	• Utterance of one-word sentence	
2yr 4m	• Delays in language • Mild Ventriculomegaly and brain atrophy	
2yr 8m	• Difficulty in concentration • Deterioration of the motor and cognitive function	
2yr 11m		• Utterance of two-word sentence
3yr 11m	• Utterance of two word sentence	
5yr	• Mild Ventriculomegaly and Brain atrophy (no exacerbation)	

- **Age equivalent scores (AE) of sibling 2 remained normal and exceeded 42 months**
- **There was no obvious problems of somatic symptoms in sibling 2**

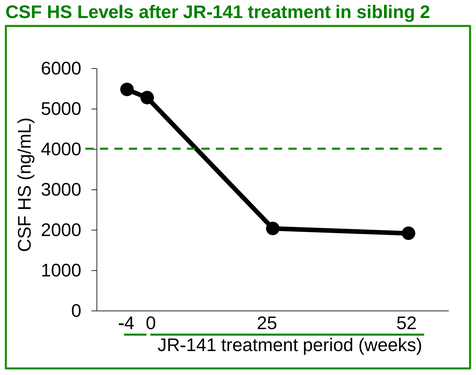
Time-course Changes in the CSF HS Concentrations in Sibling 2

Baseline CSF HS Levels in the patients in the phase II/III study



- Baseline CSF HS levels differentiate patients between severe and attenuated phenotype

CSF HS Levels after JR-141 treatment in sibling 2



- Treatment with JR-141 reduced CSF HS levels in sibling 2 by 63.6% and to a level typical for attenuated patients

Summary

- Two sibling cases of MPS-II with shared genetic mutations are reported.
- Developmental Quotients at 3 years and 11 months of age were 54 in sibling 1, and 104 in sibling 2; i.e. notable preservation of neurocognitive development in sibling 2.
- Age equivalent score of sibling 2 remained normal, and exceeded 42 months (above the upper limit of severe MPSII patients in the natural history studies).
- HS levels in the CSF in sibling 2 decreased by 63.6% within 52 weeks after switching to JR-141.
- The marked difference in the developmental trajectories in these siblings highlights the critical importance of early diagnosis and treatment in MPS-II, along with potential benefits of brain-penetrating ERT.

Acknowledgments

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