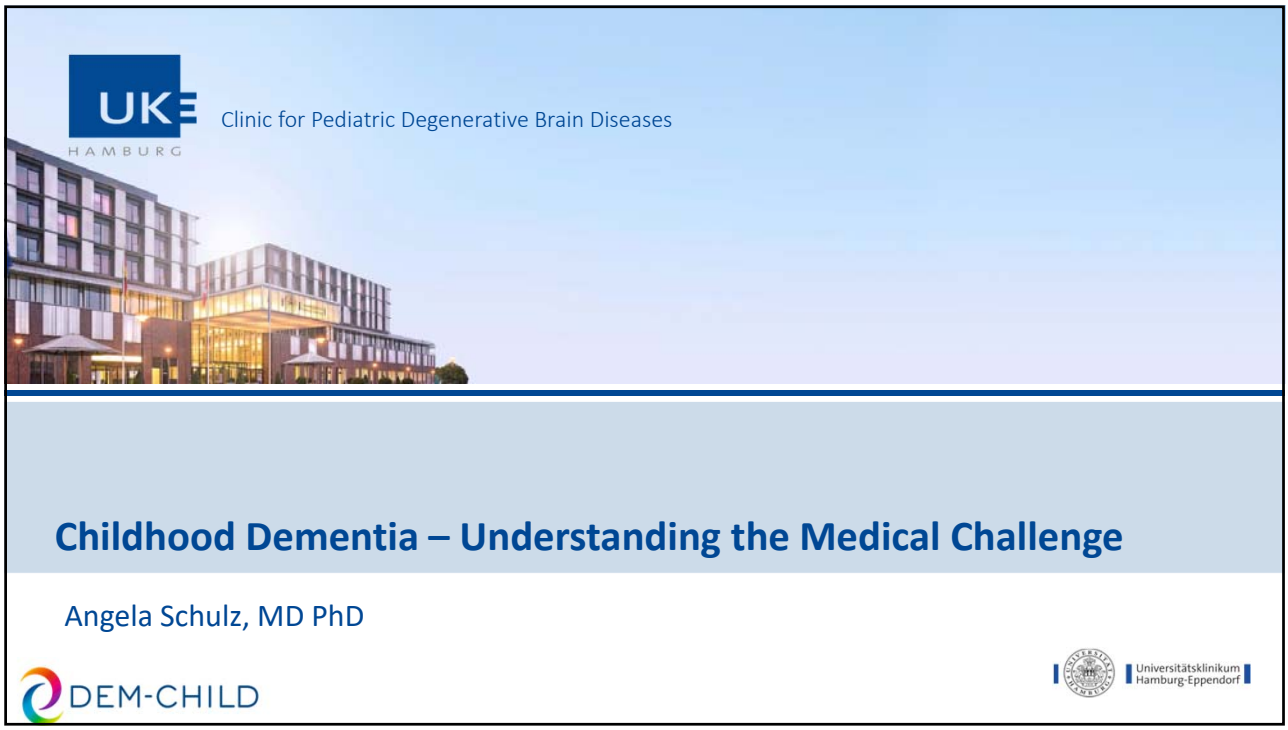

Childhood Dementia – Understanding the Medical Challenge

Angela Schulz, MD PhD

DEM-CHILD

Universitätsklinikum Hamburg-Eppendorf

UKE Hamburg- Eppendorf
Clinic for pediatric degenerative brain diseases

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DEM-CHILD

Coordination of international DEM-CHILD Patient Database

In- and outpatient clinic:

152 patients with Batten disease/year:
(national/international)

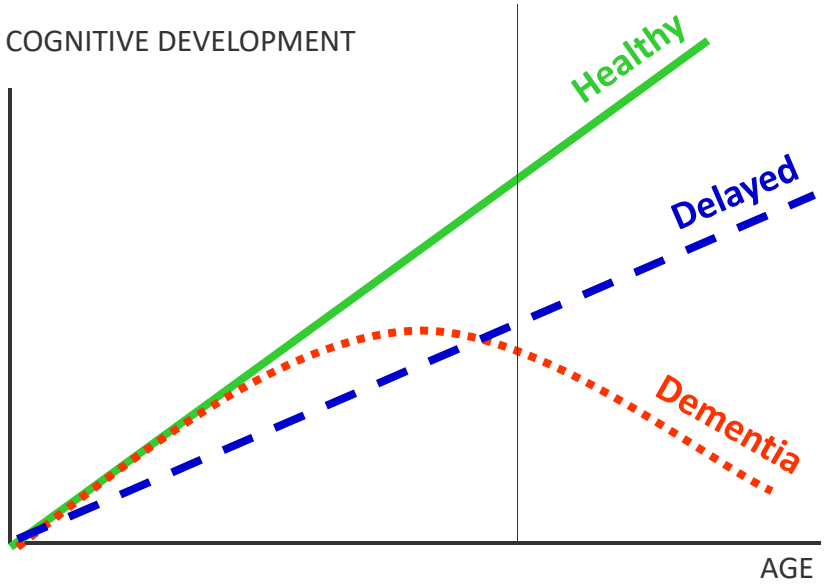
- 66 patients with CLN2 (of those 35 on ERT)
- 48 patients with CLN3
- 38 patients with CLN1, CLN5, CLN6, CLN7, CLN8
- Overall data on 219 NCL patients

DEM-CHILD

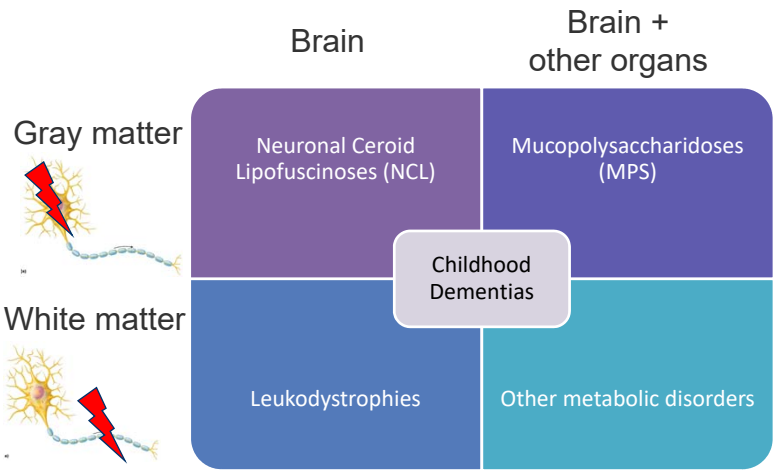
Speaker's own data

NCL, Neuronal ceroid lipofuscinosis

Childhood dementia

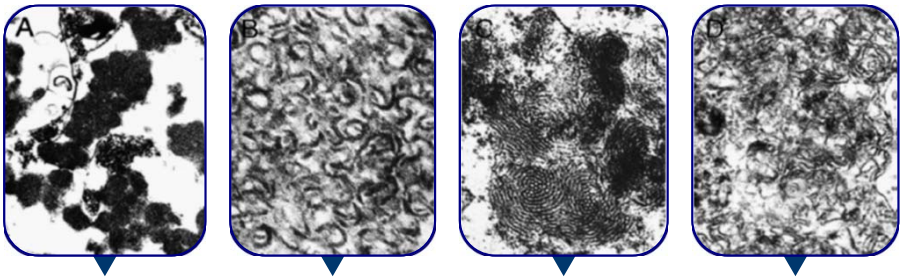


Diseases causing childhood dementia



NCL Disorders – an Overview

Lysosomal storage material in NCL disorders



Granular	Curvilinear	Fingerprint	Other
CLN1	CLN2	CLN3	

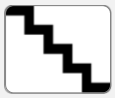
Haltia M. *Biochim Biophys Acta*. 2006;1762:850-856.

NCL Disorders – an Overview

Growing number of NCL disorders

Today we know **≈13** genetically distinct human NCL disorders
(12 have autosomal recessive inheritance)

Their clinical hallmark is the combination of



Dementia

Visual loss
due to retinopathy

Epilepsy

NCL: The most frequent cause of dementia in young persons

Schulz A, Kohlschütter A. Iranian Journal of Child Neurology. 2013;7:1-8.

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NCL: Genes and clinical onset

DEM-CHILD

	Disease	Onset				Protein	*Gene*
Soluble lysosomal enzymes	**NCL1**	Infantile	Late infantile	Juvenile	Adult	Palmityl protein thioesterase 1	*CLN1 (PPT1)*
	NCL2	Infantile	Late infantile	Juvenile / Protracted		Tripeptidyl peptidase 1	*CLN2 (TPP1)*
	NCL10	Congenital		Juvenile	Adult	Cathepsin D	*CLN10 (CTSD)*
	NCL13				Adult Kufs B	Cathepsin F	*CLN13 (CTSF)*
Other enzymes	**NCL12**			Juvenile		ATPase	*CLN12 (ATP13A2*)*
Nonenzyme proteins (function poorly understood)	**NCL3**			Juvenile		Transmembrane protein	*CLN3*
	NCL4				Adult*	Soluble cysteine string protein α	*CLN4 (DNAJC5)*
	NCL5		Late infantile	Juvenile	Adult	Soluble lysosomal protein	*CLN5*
	NCL6		Late infantile		Adult Kufs A	Transmembrane protein	*CLN6*
	NCL7		Late infantile			Transmembrane protein	*CLN7 (MFSD8)*
	NCL8		Late infantile	Juvenile EPMR		Transmembrane protein	*CLN8*
	NCL11				Adult	Progranulin	*CLN11 (GRN*)*
	NCL14	Infantile				Potassium channel protein	*CLN14 (KCTD7*)*

Adapted from Schulz A, et al. *Biochimica et biophysica acta*. 2013;1832:1801-1806.

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DEM-CHILD NCL Database Consortium

DEM-CHILD

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Oslo University Hospital

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Jon R. Ostergaard, MD
Aarhus University Hospital

Sweden
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The Queen Silivia Children's Hospital, Gothenburg

Poland
Tomas Kmiec MD
Children's Memorial Health Institute, Warsaw

Netherlands
Hippe Huidekopper, MD PhD — Erasmus Medical Center, Rotterdam
Claudia van Alfen, MD — Bartiméus Center, Dorn

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University Children's Hospital, Ankara

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Rose-Mary Boustany MD PhD
Amrican University of Beirut

France
Catherine Caillaud MD PhD
INSERM, Paris

Spain
Maria del Socorro Pérez Poyato MD
Hospital Universitario Marqués de Valdecilla, Santander

19 countries and 26 centers
Data from > 500 NCL patients

Japan
Eto Yoshikatsu, MD PhD
Tokyo Medical University

Argentina
Ines Noher de Halac, MD
Universidad Nacional de Cordoba

Brazil
Charles Lourenco, MD PhD
University of São Paulo

Germany
Angela Schulz, MD , Co-ordinator
University of Hamburg

Italy
Alessandro Simonati MD — University of Verona
Nicola Specchio MD — Ospedale Bambino Gesù, Rome

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Ruth Williams, MD — GSTT, London
Paul Gissen MD — Great Ormond Street Hospital

Finland
Laura Aberg
Folkhälsan, Helsinki

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PGIMER, Chandigarh

Ron Crystal, MD PhD
Weill Cornell Medical College, New York

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University of Rochester

Emily de los Reyes, MD
Nationwide Children's Hospital, Columbus

Katherine Taub, MD
Children's Hospital of Philadelphia

Kathryn Swobody, MD
Massachussetts General Hospital, Boston

http://www.dem-child.eu/index.php/consortium.html, accessed October 2018

Aims of DEM-CHILD

International collaboration

- To collect precise natural history data of all NCL types
- To improve early diagnosis of NCLs
- To optimise standard of care for patients
- To establish evaluation tools for experimental therapies

…and make these data available to third parties (scientists and industry) in a transparently regulated and time-effective process

http://www.dem-child.eu/index.php/consortium.html, accessed October 2018

DEM-CHILD NCL Patient Database – Support

Patients and Families

Family Associations

Foundations

Gouvernment funded research grants

Industry Funded Independent Research Grants

http://www.dem-child.eu/index.php/consortium.html, accessed October 2018

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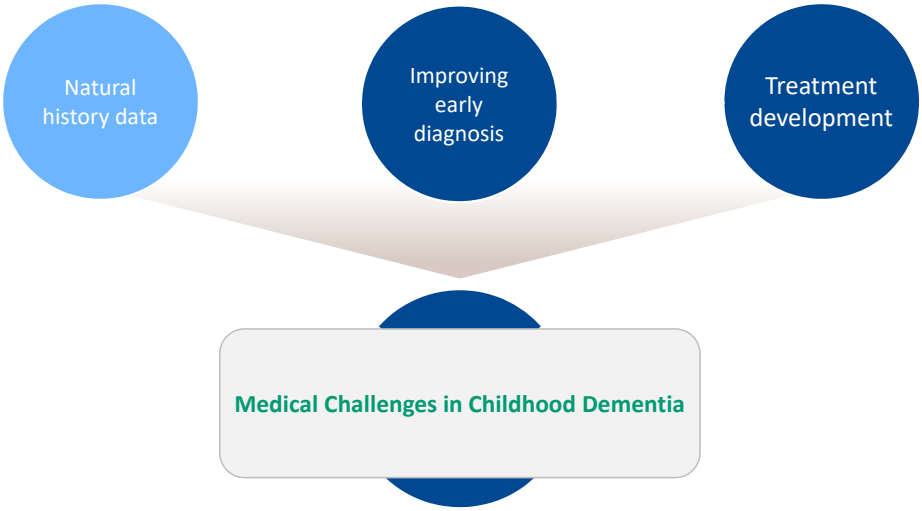

Speaker's own illustration

CNS, central nervous system

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NCL: Genes and clinical onset

DEM-CHILD

	Disease	Onset				Protein	*Gene*
Soluble lysosomal enzymes	**CLN1**	Infantile	Late infantile	Juvenile	Adult	Palmityl protein thioesterase 1	*CLN1 (PPT1)*
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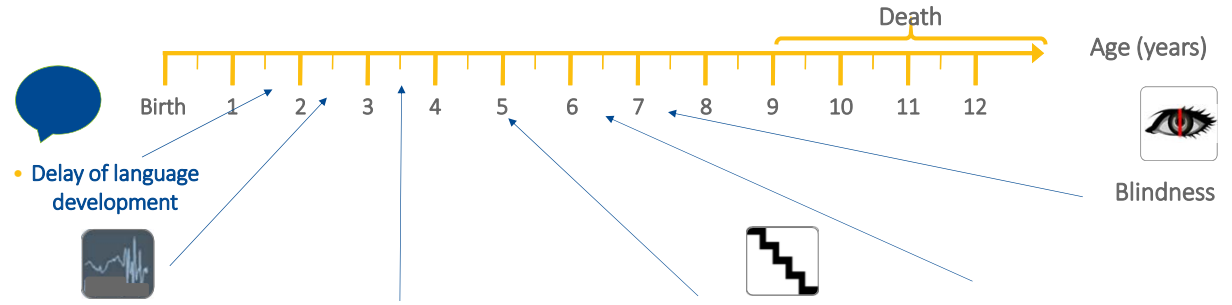
	CLN14	Infantile				Potassium channel protein	*CLN14 (KCTD7*)*

Adapted from Schulz A, et al. *Biochimica et biophysica acta*. 2013;1832:1801-1806.

Clinical Presentation: CLN2 Disease*



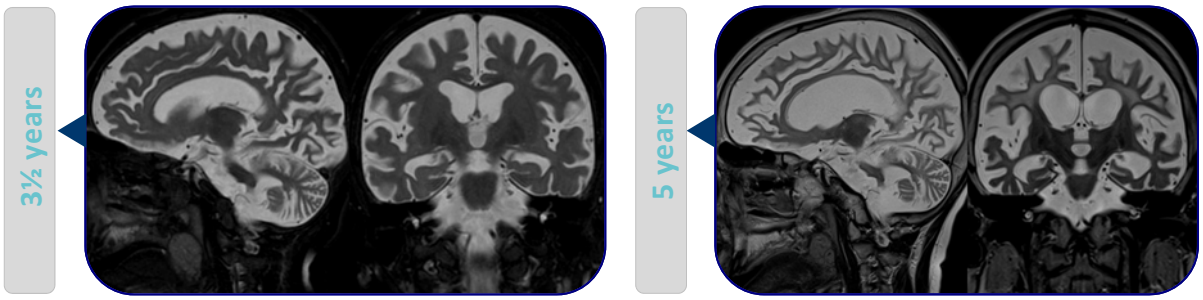
Placeholder for Patient Videos

Seizures Ataxia Psychomotor decline Bedridden

Speaker's own patient, images used with permission

*Late-infantile phenotype

Progressive brain atrophy in CLN2 disease



Speaker's own patient, images used with permission

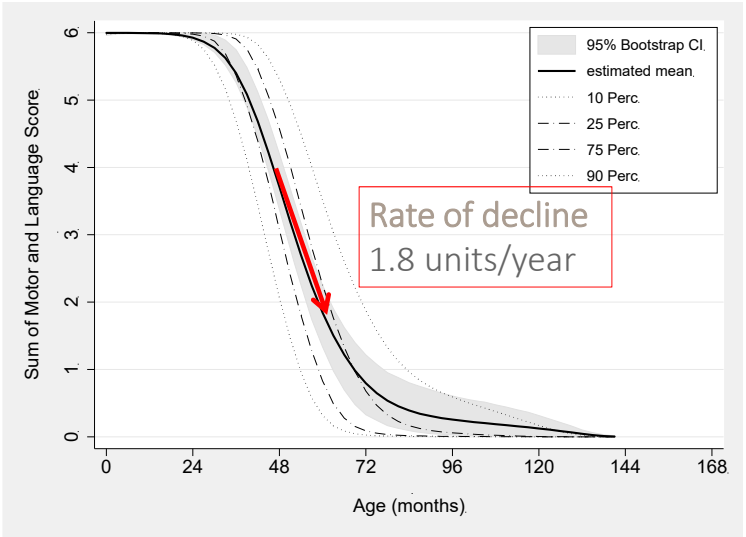
Clinical Scoring for Disease Severity in Late Infantile NCL (CLN2): Hamburg Scale

Functional Category
Motor function
Language
Visual function
Seizures

Each functional category is	scored from 0-3
Normal function	= SCORE 3
Slightly abnormal	= SCORE 2
Severely abnormal	= SCORE 1
No function left	= SCORE 0

Steinfeld R, et al. *Am J Med Genet* 2002;112:347-54.

Motor & Language Score: Rate of Decline



Nickel M, et al. *Lancet Child Adolesc Health*. 2018;2:582-590.

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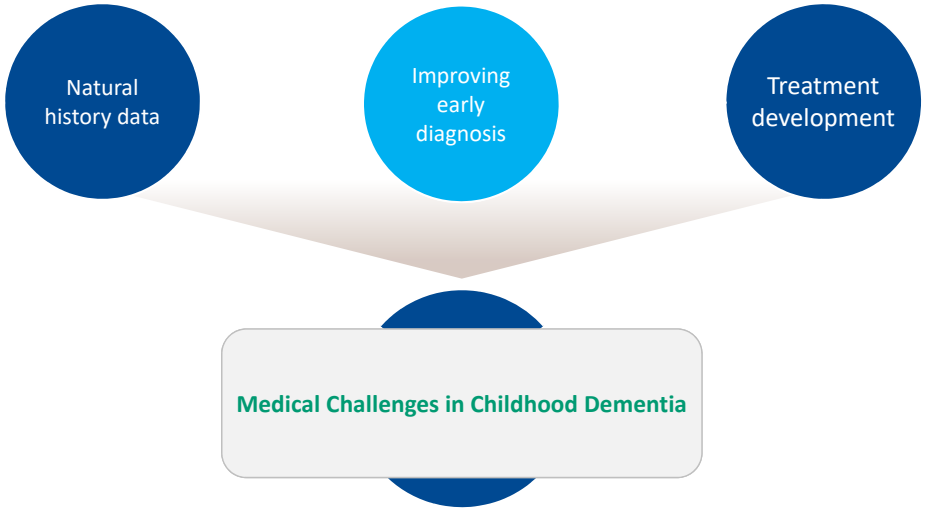

Speaker's own illustration

CNS, central nervous system

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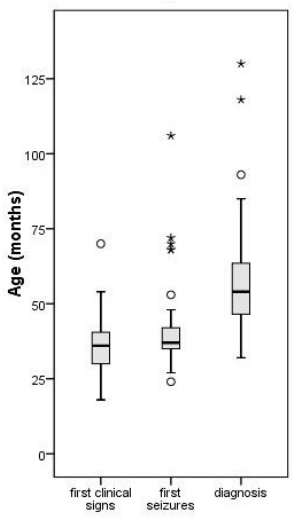
CLN2 Disease: Diagnostic challenge

DEM-CHILD

Age of First Clinical Symptom, Seizure, and Diagnosis



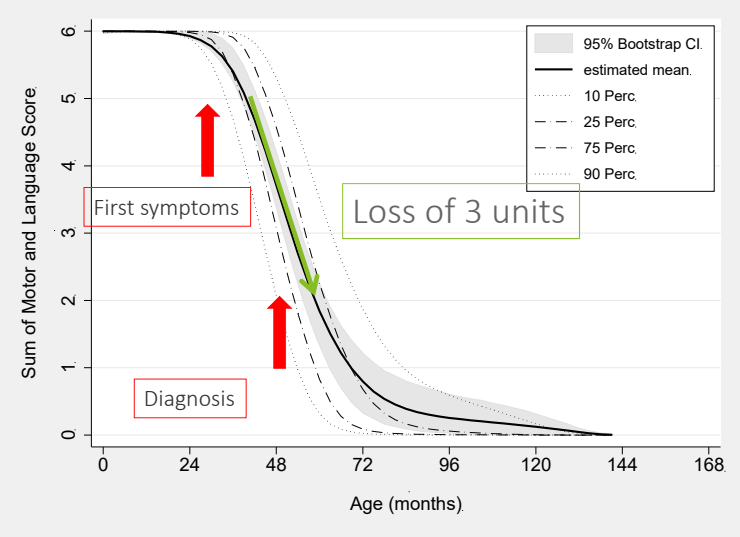
Age at diagnosis
56 (±18.6) months

Delay of 21 months

Age at first clinical symptoms (seizures)
35 (±9.6) months

Nickel M, et al. *Lancet Child Adolesc Health*. 2018;2:582-590.

Motor & Language Score: Effect of delayed diagnosis



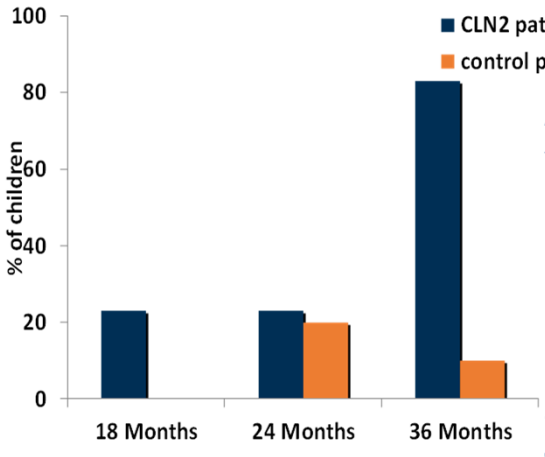
Nickel M, et al. *Lancet Child Adolesc Health*. 2018;2:582-590.

First symptoms leading to diagnosis

First clinical sign	% of patients
Seizures	73
Language delay	59
Motor difficulty	45
Behavioural abnormality	23
Dementia	9

20 Nickel M, et al. Presented as poster at the 12th Annual WORLD*Symposium*; February-March 2016; San Diego, CA, USA

Language Developmental Delay in 36 CLN2 Patients



A delay of language development was defined by the following criteria

Parents' statement: abnormal initial language development

First single words at 18 months (or later)/never

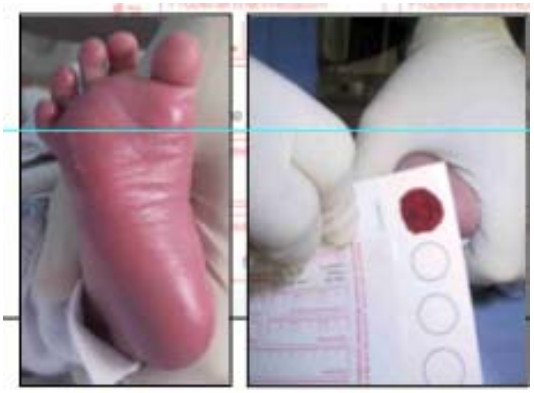
First two-word sentences at 24 months (or later)/never

First whole sentences at 36 months (or later)/never

83% of patients showed a delay in the development of expressive language skills

Nickel M et al. *Lancet Child Adolesc Health.* 2018;2:582–590.

Language Developmental Delay in 36 CLN2 Patients



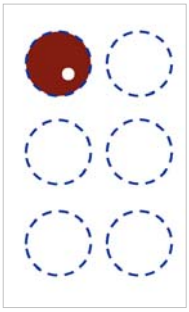
For children who present with new onset seizures,
ASK
about early language delay
and
TEST for CLN2

Nickel M et al. *Lancet Child Adolesc Health.* 2018;2:582–590.

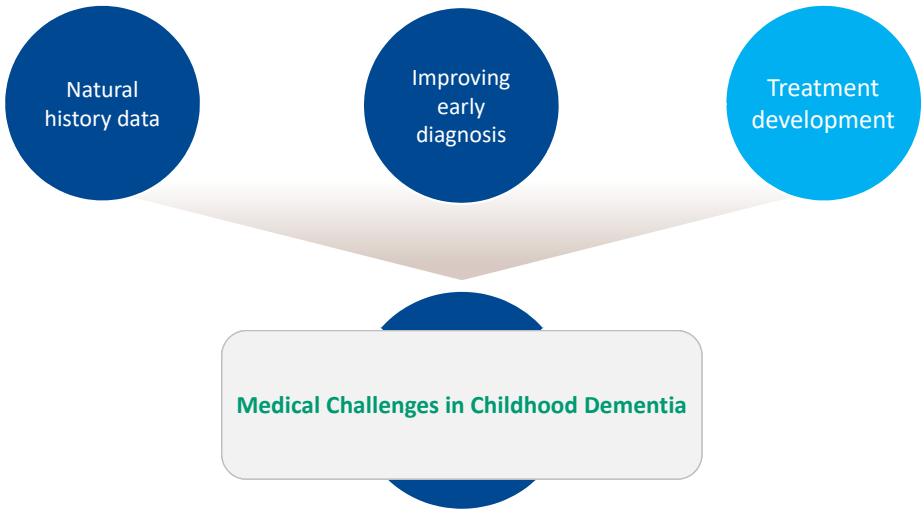
New enzymatic test for NCLs

Automated triple enzyme testing for CLN1, CLN2, and CLN10

- Innovative:
  - Mass Spectrometry of **dry blood spots**
  - High-throughput technique
- Time- and cost-effective: Price per sample ca. 50 €



Pzybylski M, Cozma C, **Schulz A**, Braulke T. Method for the diagnosis of neuronal ceroid lipofuscinoses. Eur. Patent Application. (EP14000667)



Speaker's own illustration

CNS, central nervous system

Experimental Therapies – Clinical Trials in Patients

NCL subtype	Treatment approach	Status	Responsible
CLN1	Stem Cell Therapy	Completed	StemCells, Inc.
	Cystagon (substrate reduction)	Completed	NICHD, Bethesda
CLN2	ERT with BMN-190 (Intraventricular)	Active Approved	BioMarin
	Gene therapy AAVrh10 (Intracerebral)	Recruiting	WCMC, NY
	Gene therapy AAV2 (Intracerebral)	Completed	WCMC, NY
	Stem Cell Therapy	Completed	StemCells, Inc.
CLN3	Immune modulation, Mycophenolate	Completed	Univ. Rochester, NY
CLN6	Gene therapy AAV9 (Intrathecal)	Recruiting	Amicus (Columbus, OH)
ALL	Intrathecal Administration of Human Umbilical Cord Blood-Derived Oligodendrocyte-Like Cells	Recruiting	Duke Univ., NC

Speaker's own summary overview

Red: Trials using DEM-CHILD natural history data as controls__

Experimental Therapies – Clinical Trials in preparation

NCL subtype	Treatment approach	Sponsor
CLN1	Gene therapy (scAAV9, intravenous)	Abeona
CLN2	Gene therapy (AAV2, ependymal)	CHOP
CLN2	PLX-100 (increased CLN2 mRNA expr enhancing lys biogenesis)	Polaryx
CLN3	Gene therapy (scAAV9, intravenous)	Abeona
CLN3, CLN6, CLN8	Gene therapy (scAAV9, intracisternal)	Amicus
CLN3	XN001 (enhancing CRMP2 fct, autophagy efficacy)	Xonovo
CLN3	Trehalose (enhancing autophagy)	Beyond Batten Disease Foundation
	AND?	

Speaker's own summary overview

Red: Trials using DEM-CHILD natural history data as controls__

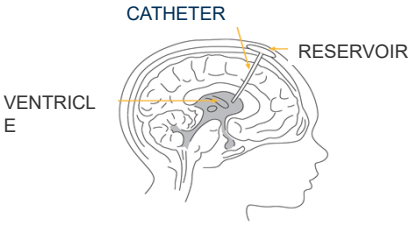
Approved: Cerliponase Alfa Treatment for CLN2 Disease

Cerliponase alfa is a recombinant human form of tripeptidyl peptidase 1 enzyme (rhTPP1)

Does not cross the blood-brain barrier (66 kDa)

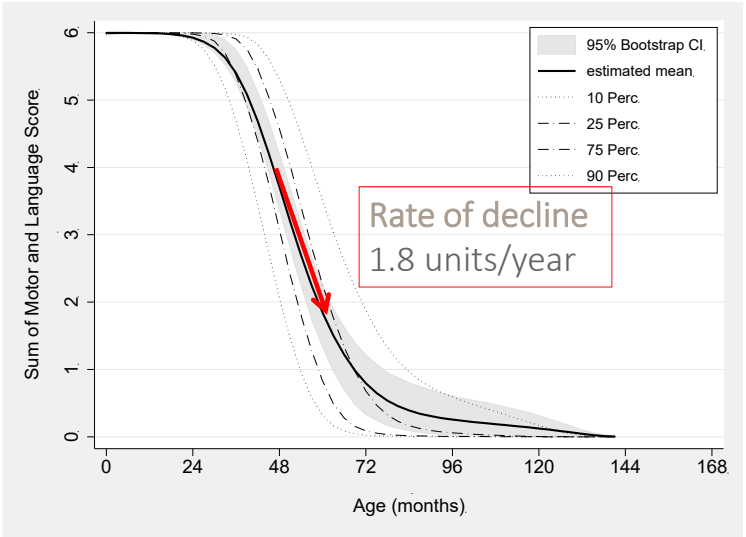
Administered through a Rickham or Ommaya device into the lateral cerebral ventricles

300 mg dose every 14 days via intracerebroventricular (ICV) infusion over ~ 4 hours



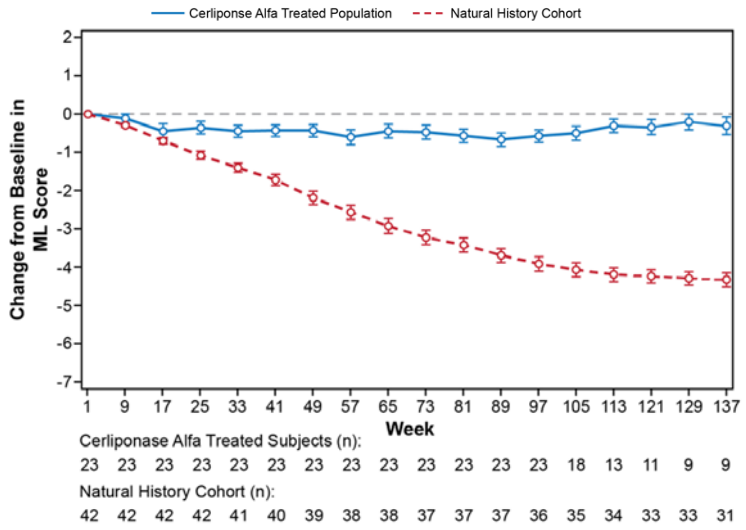
Schulz A, et al. *N Engl J Med* 2018;378:1896-1907.

Motor & Language Score: Rate of Decline



Nickel M, et al. *Lancet Child Adolesc Health*. 2018;2:582-590.

Motor-Language Score (0-6) Change from Baseline[a]: Compared to Natural History

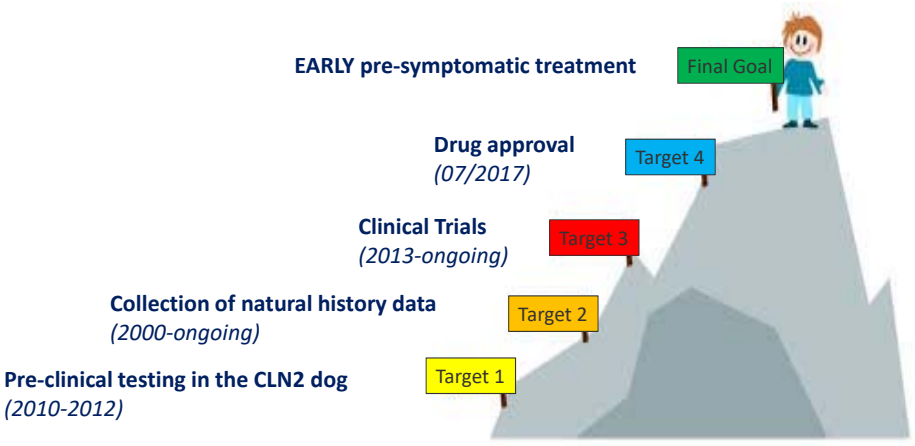


After **48 weeks** of therapy:
Treatment difference is 1.8 points in favor of treated subjects

After **96 weeks** of therapy:
Treatment difference is 3.3 points in favor of treated subjects

Schulz A, et al. *N Engl J Med* 2018;378:1896-1907.

a Rate of decline for 201/202 based on change from 300 mg baseline, at last assessment



KINDER UKE DEM-CHILD

Why early diagnosis and early treatment matter

Speakers' own opinion.

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Family A –Sister age 6 yrs – no treatment

DEM-CHILD

Placeholder for Patient Video

Family A – Video Brother age 7 yrs – 4 years tof reatment

Placeholder for Patient Video

33

Thank you!

Patients & Families

Fund rising

Research Grants

VV-MEDCOM-9094
Date of preparation: October 2018