European Reference Network for rare or low prevalence complex diseases

Network Neurological Diseases (ERN-RND)

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European Reference Network for rare or low prevalence complex diseases

Network Neuromuscular Diseases (ERN EURO-NMD)

Webinar – 11.October 2022

Krabbe disease – natural history and treatment options

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***on behalf of the 'lysosomal team'**
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Ludger Schöls – Neurology
Ralf Husain – Jena
Volkmar Gieselmann - Bonn

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Learning objectives

- By the end of this webinar you will be able to:

  - discuss the different forms and dynamics of Krabbe‘s disease
  - identify the first symptoms of the disease
  - know about the role of neuroimaging, biochemistry and genetics for diagnosis and counselling
  - understand the treatment options

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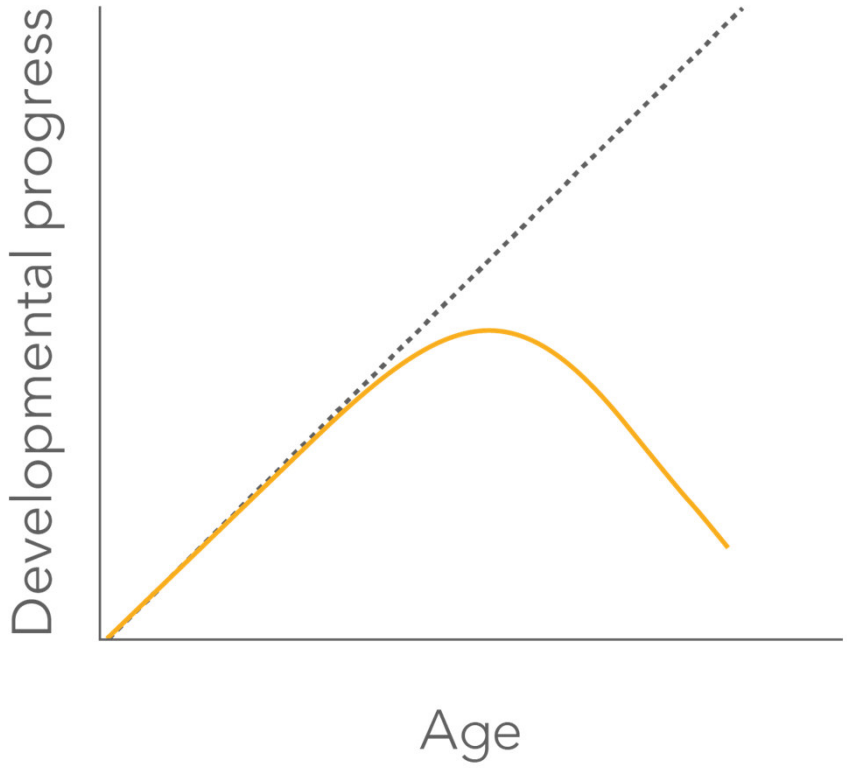
Webinar outline

- Introduction
- Methods
- Natural history and imaging findings
- Diagnostic procedures
- Treatment options

Two histories – what do they have in common?

Normal development during the first 4 months.
The child then gets irritable, often cries and gets into opisthotonus.
It does not grasp any more, has less visual contact
- marked irritability and tone increase
- peripheral neuropathy

Normal development into the 2nd decade.
Then gait appears a bit strange, ‚staggery', clumsy (retrospectively hollow feet since 4 yrs)
- Demyelinating polyneuropathy
- Pyramidal signs



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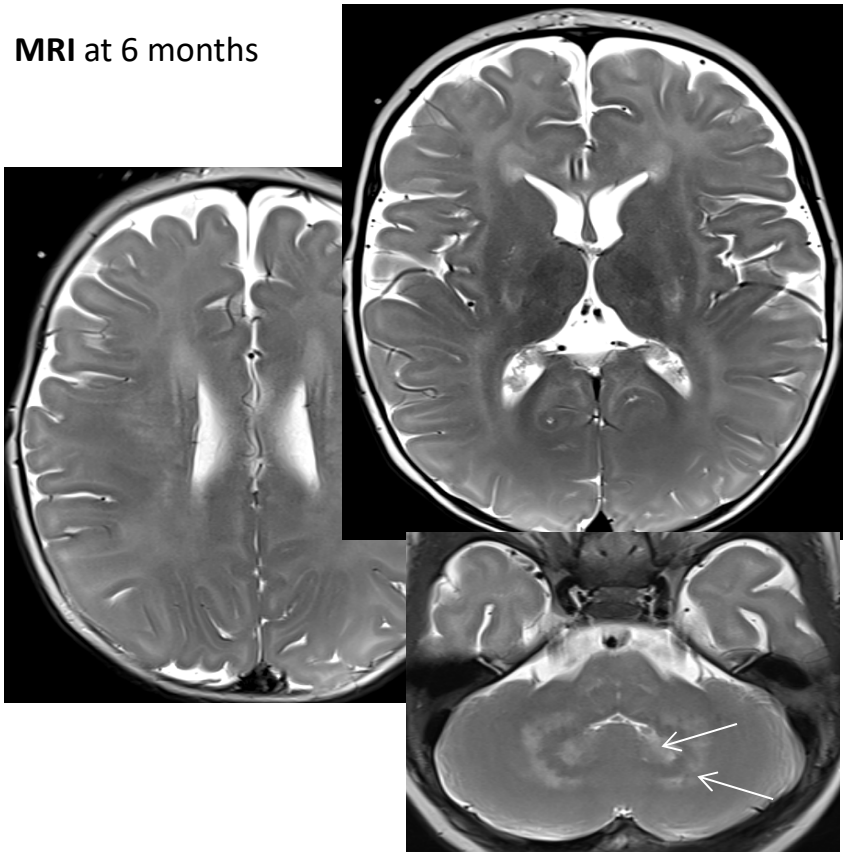
MRI at 6 months



Normal development into the 2nd decade.
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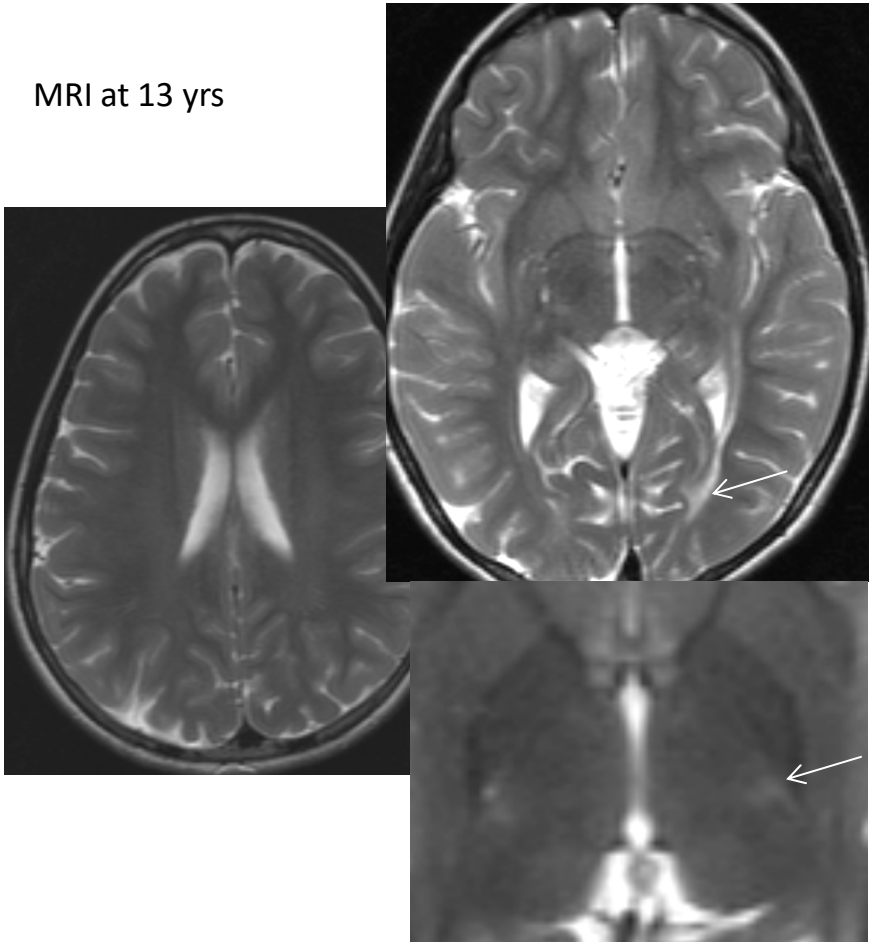
- Demyelinating polyneuropathy
- Pyramidal signs

MRI at 13 yrs



Morbus Krabbe
globoidcell leucodystrophy

- rare lysosomal storage disorder
- mutations in the GALC gene lead to a deficiency of the enzyme β-Galactocerebrosidase

Suzuki und Suzuki, 1970, Proceedings of the National Academy of Sciences of the United States of America

- Classical infantile form:
  early and rapid progression lead to an early death

Duffner et al. 2011 Pediatric Neurology; Bascou et al. 2019 Orphanet J Rare Dis

- Other disease courses are less well known

Kolodny 1991 Dev Neurosci; Loonen et al. 2004 Neuropediatrics; Duffner et al., 2012 Pediatric Neurology, Pediatric Neurology; Debs et al 2013 J Inherit Metab Dis.; Hosain et al 2014 Gene; Bascou et al. 2018 Orphanet J Rare Dis.

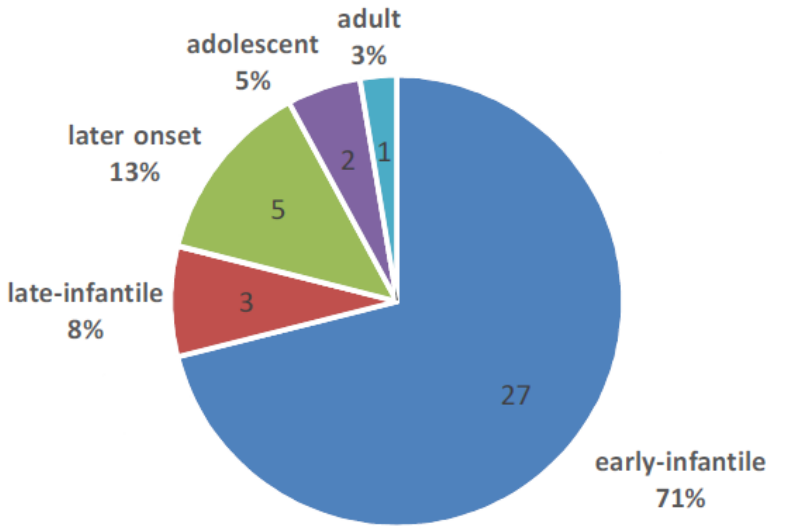
Data and methods

- Collection of developmental milestones (gain and loss of motor function, language and cognition) by means of a standardized questionnaire.
- Evaluation of MRIs with
  - A standardized Krabbe score [Loes et al., 1999, *AJNR*]

  and
  - Classification to patterns according to Abdelhalim et al., 2014, *Pediatric Neurology*
- Clinical data of 38 patients
- MRI data: 40 MRIs of 27 patients

Onset

Frequency distribution all forms of Krabbe

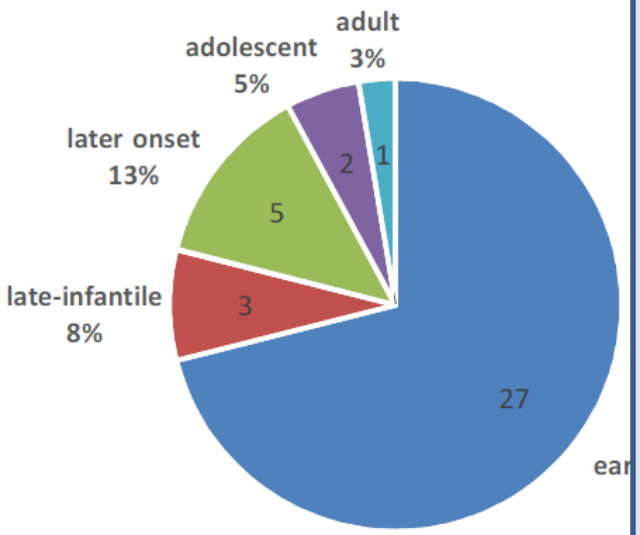


Onset	
early-infantile	0 to 6 months
late-infantile	7 to 12 months
later onset	13 mon. to 10 years
adolescent	11 years to 20 years
adult	from 21 years on

Fig 1 from Krieg et al. Orphanet Journal of Rare Diseases (2020) 15:243

Onset

Frequency distribution all forms of Krabbe



nearly 80% infantile

122 patients
62% early infantile onset,
10% onset at 7-12 months (late infantile),
22% onset at 13 months to 10 years (later onset),
5% manifested adolescent/adult onset

Duffner et al., 2012 Pediatric Neurology (data coll from 1997)

data from **96 published cases**
higher incidence of adult onset cases after 2010;
1981–1985 (n=6)
83.3% early infantile
2011–2015
37.8% early infantile,
25.6% in the late infantile,
13.3% in the juvenile,
23.3% in the adult onset group
KOMATSUZAKI et al *Genetics in Medicine, 2019*

Fig 1 from Krieg et al. Orphanet Journal of Rare Diseases (2020) 15:243

Symptoms at onset

symptoms which led to diagnostic identification:

Early symptoms at infantile onset (0 to 12 months)

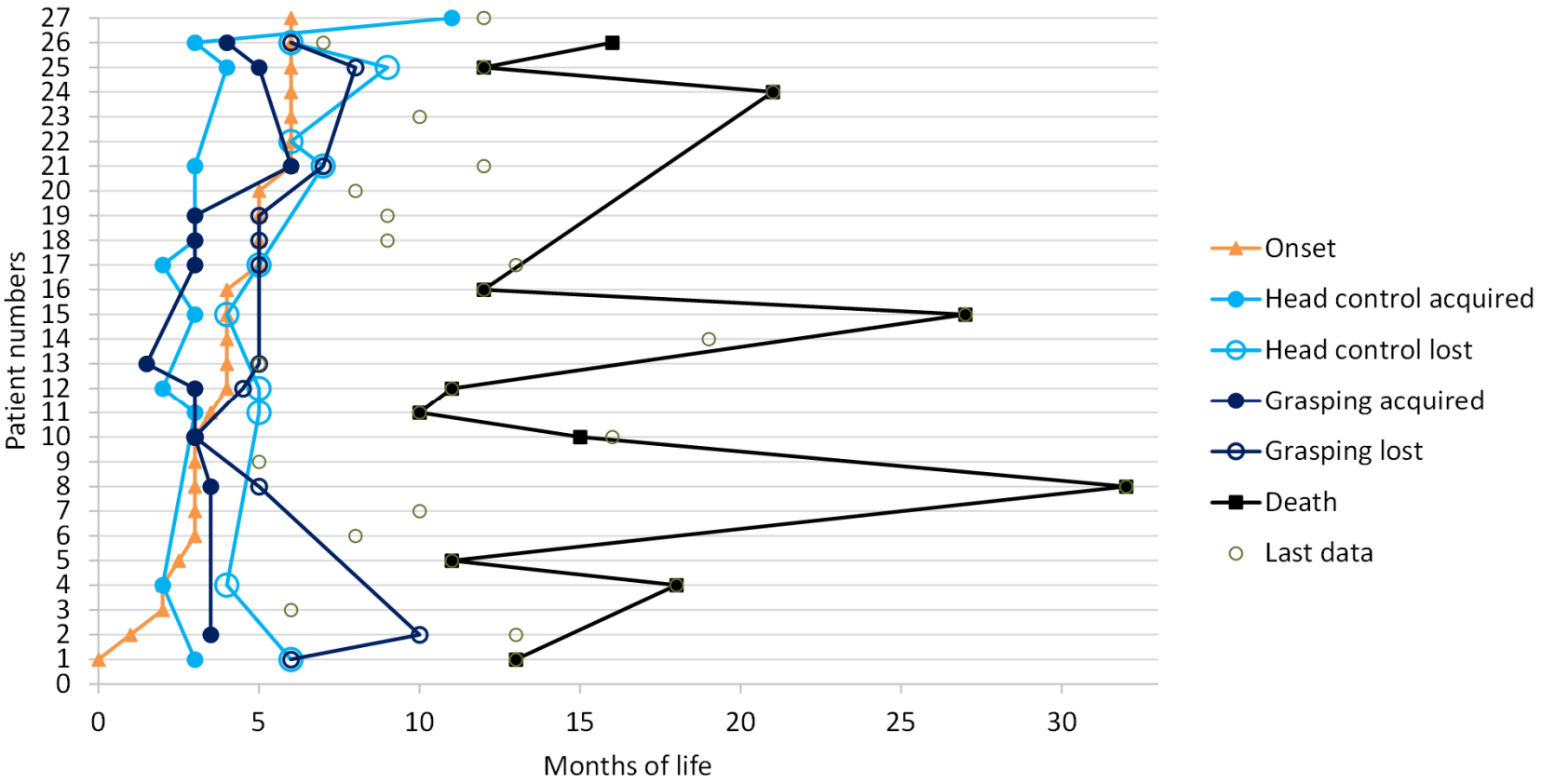
→ 1.	Agitation/Irritability	24/30	80%
2.	Abnormalities in movement pattern and general development regression	19/30	63%

Early symptoms at a later onset (from 13 months on)

→ 1.	Gait disorder/Abnormalities in movement pattern	8/8	100%
2.	Abnormalities in fine motor skills	5/8	63%
3.	General development regression	5/8	50%

Clinical course of disease

early infantile



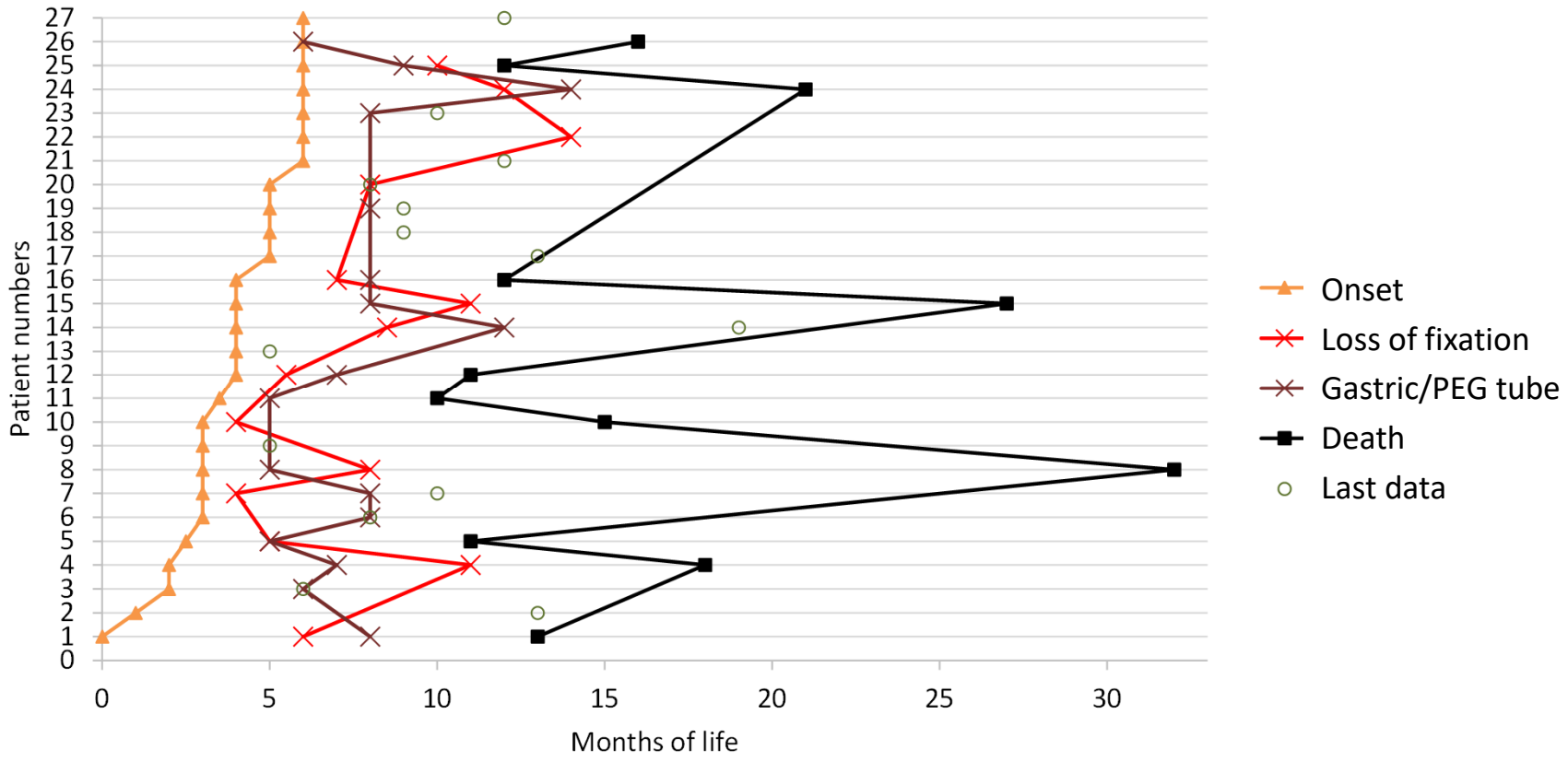
Early milestones achieved, but then quickly lost

Death usually before second birthday

Fig 2 from Krieg et al. Orphanet Journal of Rare Diseases (2020) 15:243

Clinical course of disease

early infantile

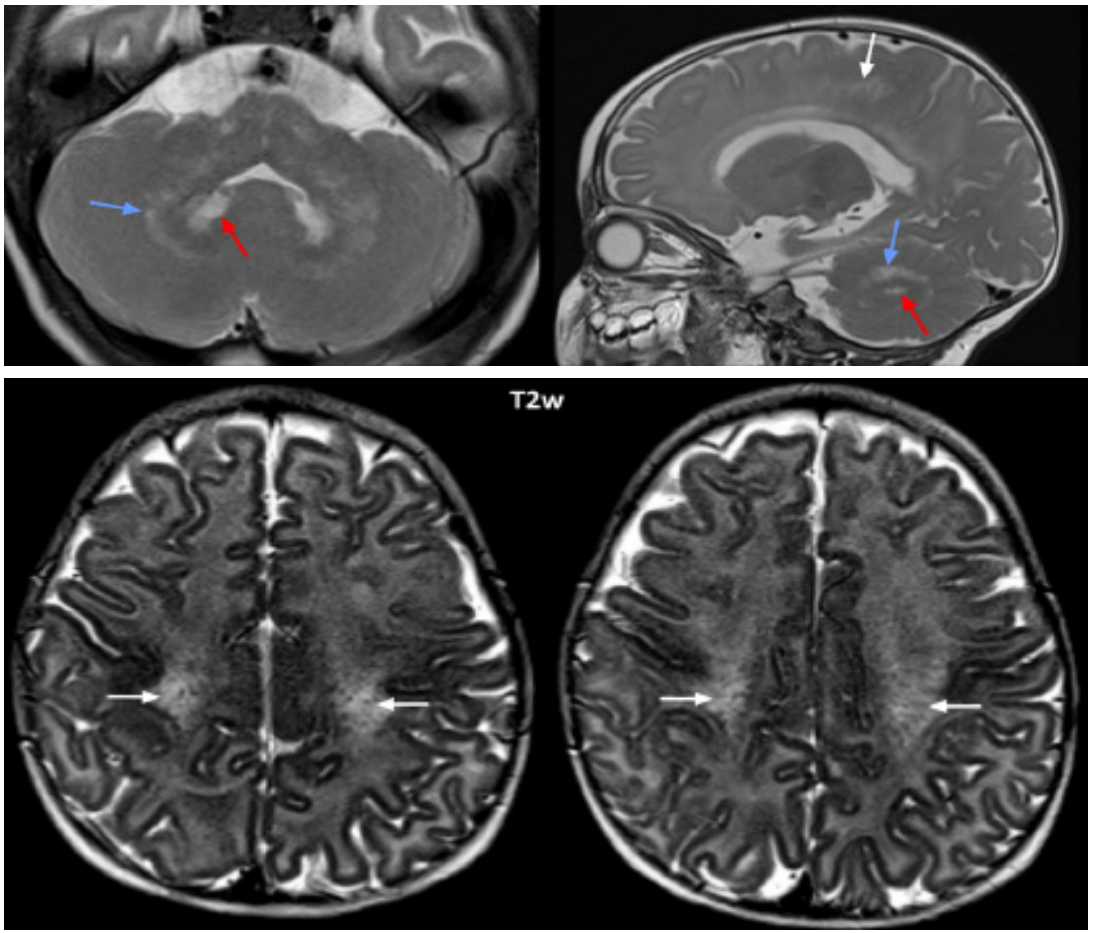


Early signs: loss of fixation, need for gastric tube

Fig 3 from Krieg et al. Orphanet Journal of Rare Diseases (2020) 15:243

MRI – pattern - early

early infantile

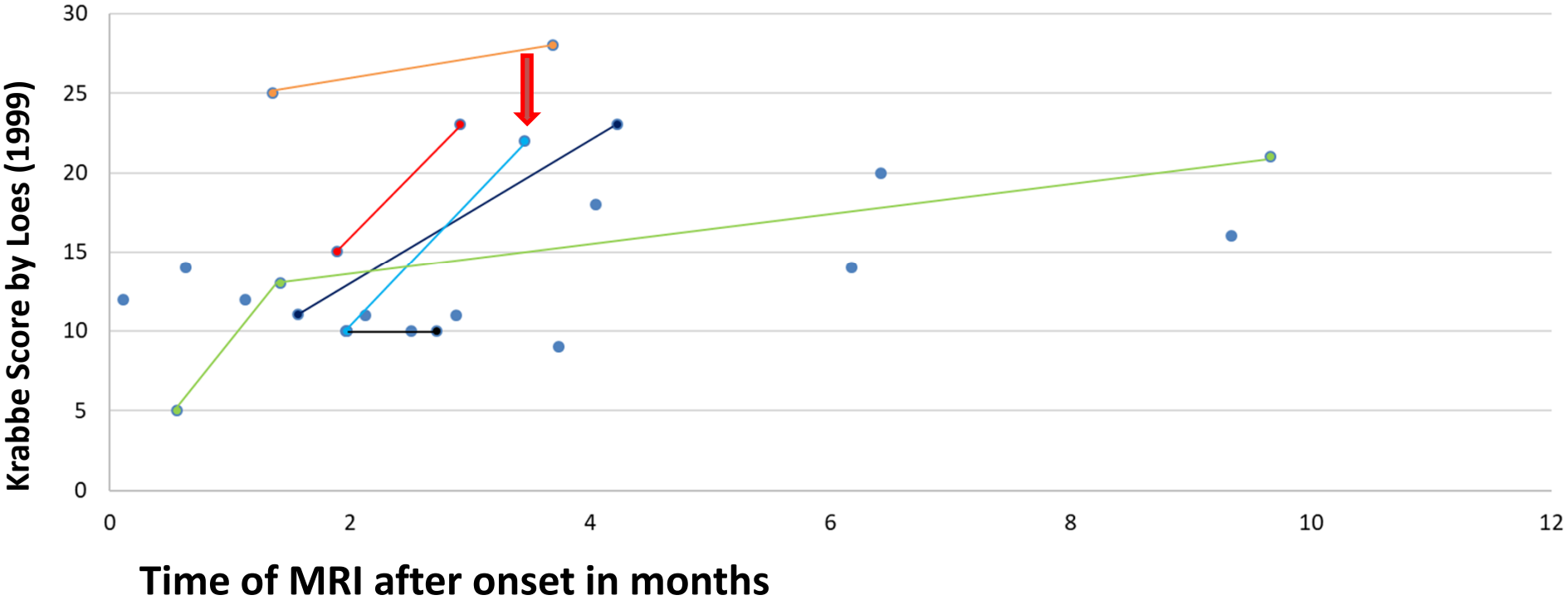


Age at MRI 5 months, onset 2 months.

- **White matter**
  Central region
- **Dentate nucleus and cerebellar white matter**
- **Corpus callosum**
- Pyramidal tract

MRI–score - course

early infantile

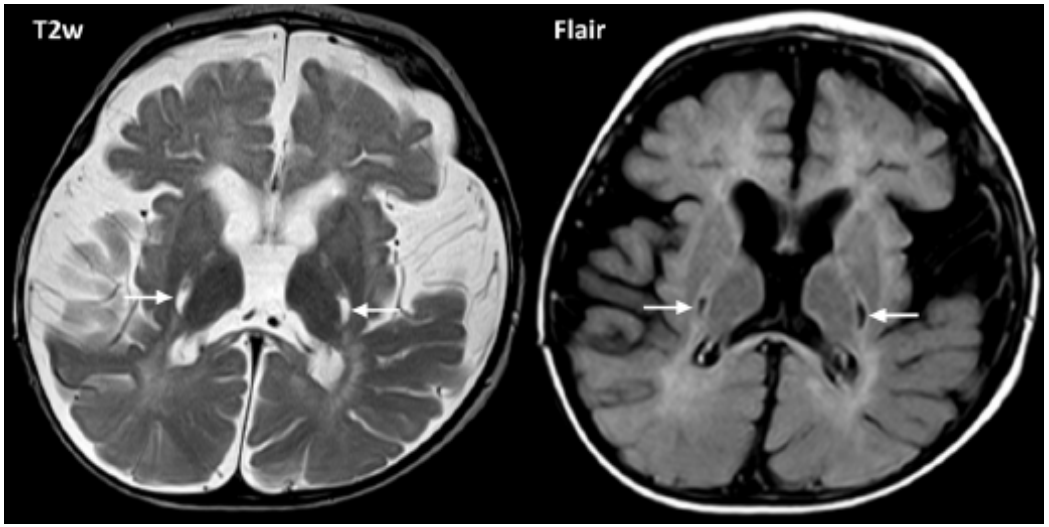


In particular cases the score can deteriorate extremely within a few weeks.
One child f.ex. showed a deterioration from 10 to 22 points within 6 weeks.

Fig 5 from Krieg et al. Orphanet Journal of Rare Diseases (2020) 15:243

MRI – pattern - late

early infantile

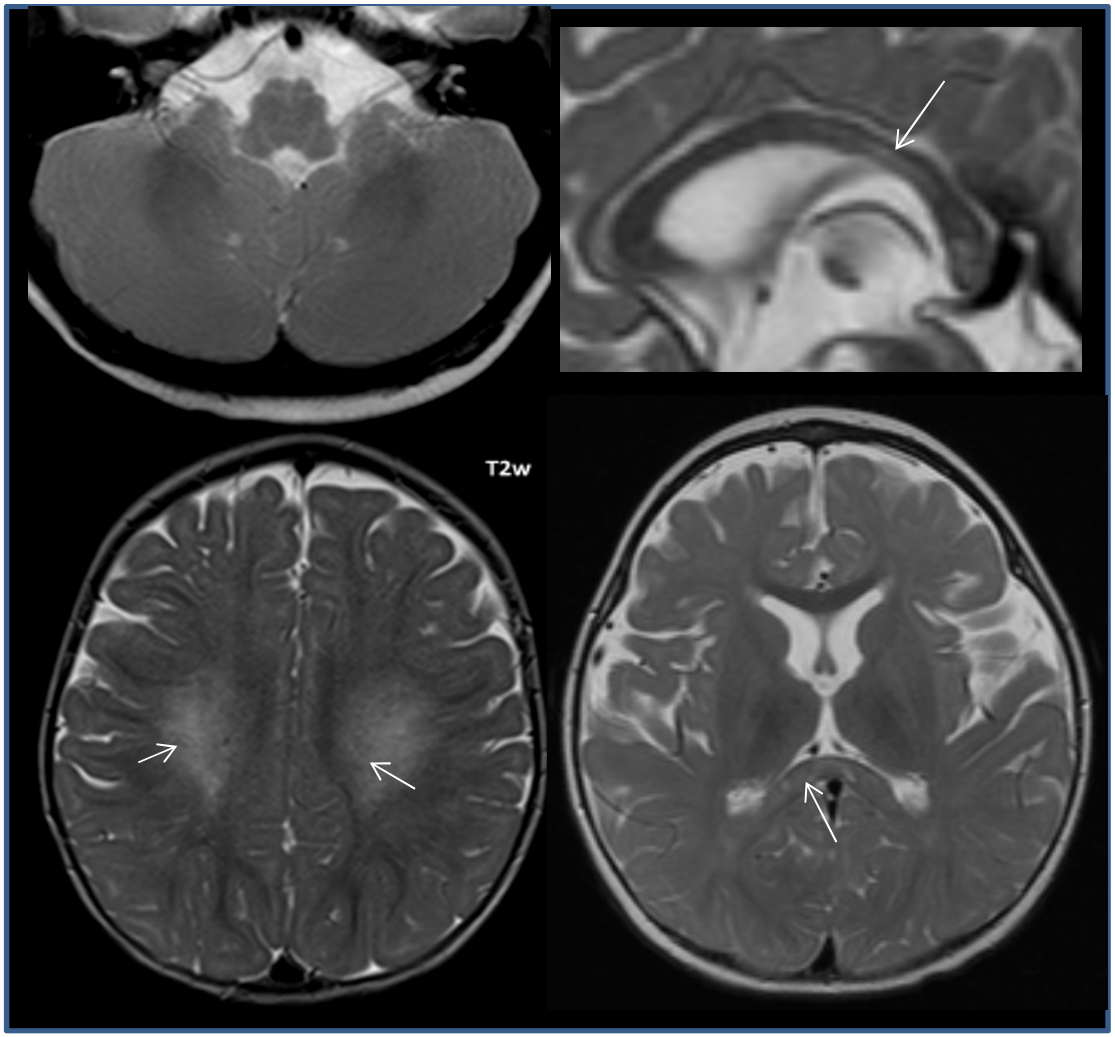


Age at MRI 8 months, onset 4 months.

- cystic degeneration of the pyramidal tract
  - T2w hyperintense
  - Flair hypointense
- global atrophy
- Extensive white matter involvement

MRI - pattern

late infantile

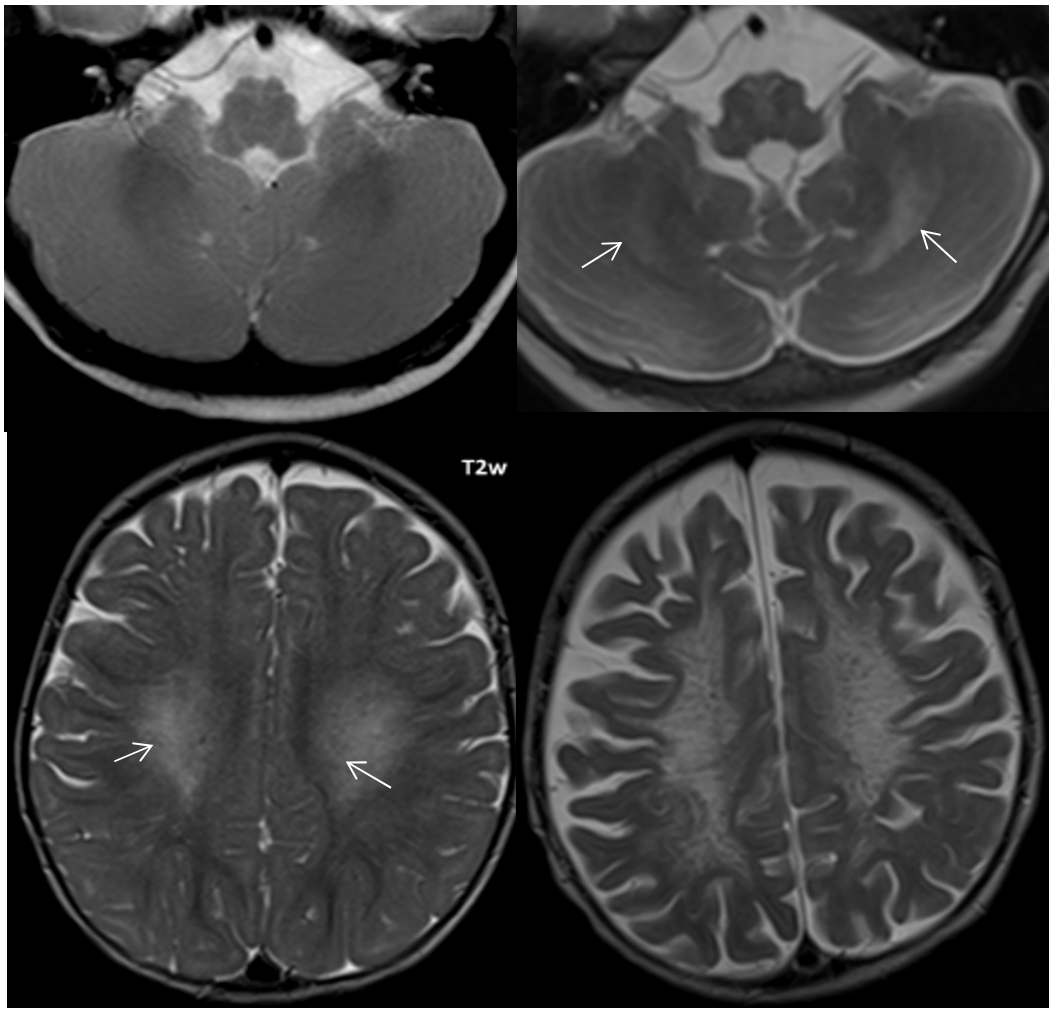


Age at MRI 12 months onset 9 months

- White matter Central region
- Corpus callosum
- Pyramidal tract
- Cerebellar white matter without dentate nucleus

MRI - pattern

late infantile



Age at MRI 12 months Age at MRI 19 months
Onset 9 months

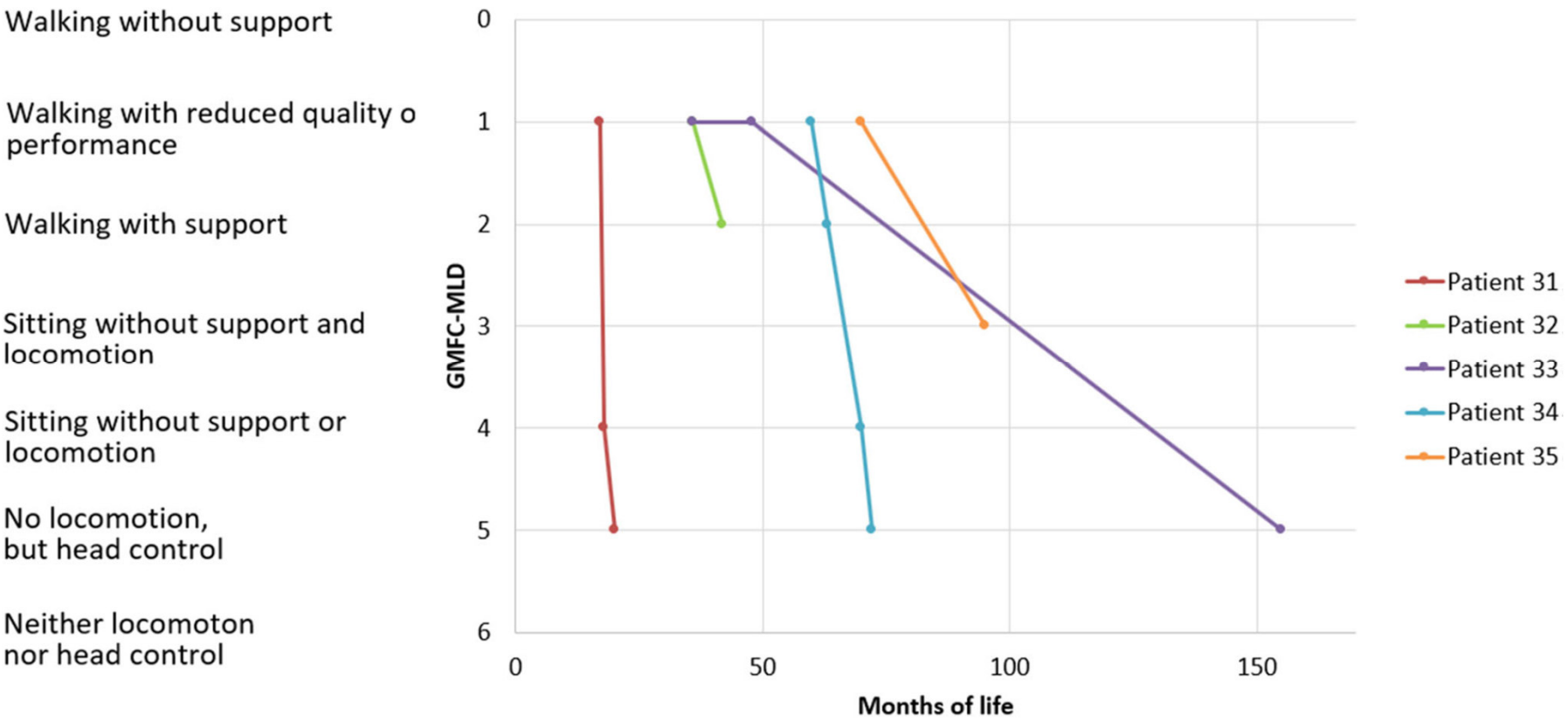
- White matter
  Central region
- Corpus callosum
- Pyramidal tract
- Cerebellar white matter without dentate nucleus

affected later

- Severe white matter changes
- atrophy

Clinical course of disease

later onset



Individual courses of gross motor function according to the GMFC-MLD

Fig 4 from Krieg et al. Orphanet Journal of Rare Diseases (2020) 15:243

Clinical course of disease

later onset

32 patients,
9 onset 12 months – 3 yrs

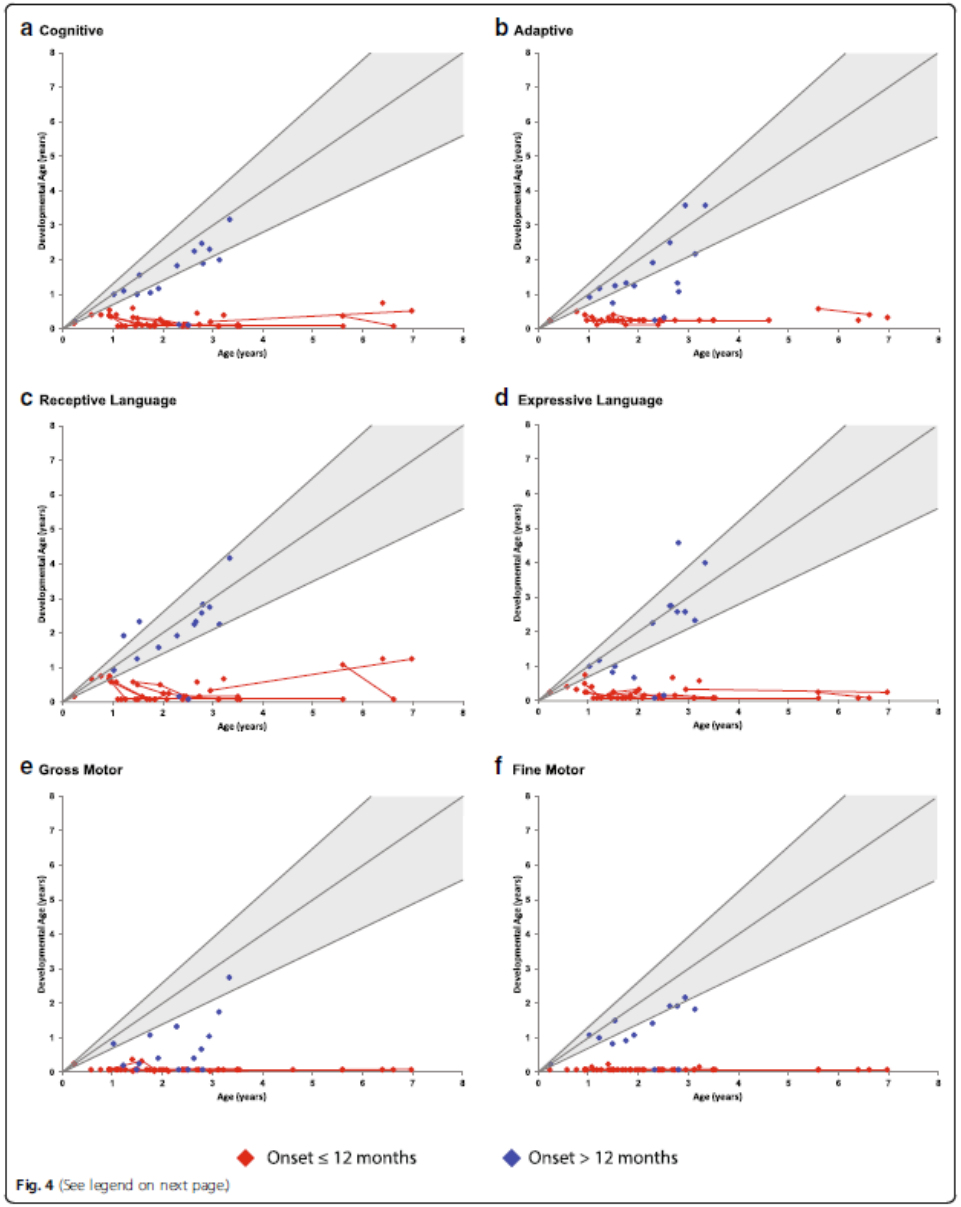
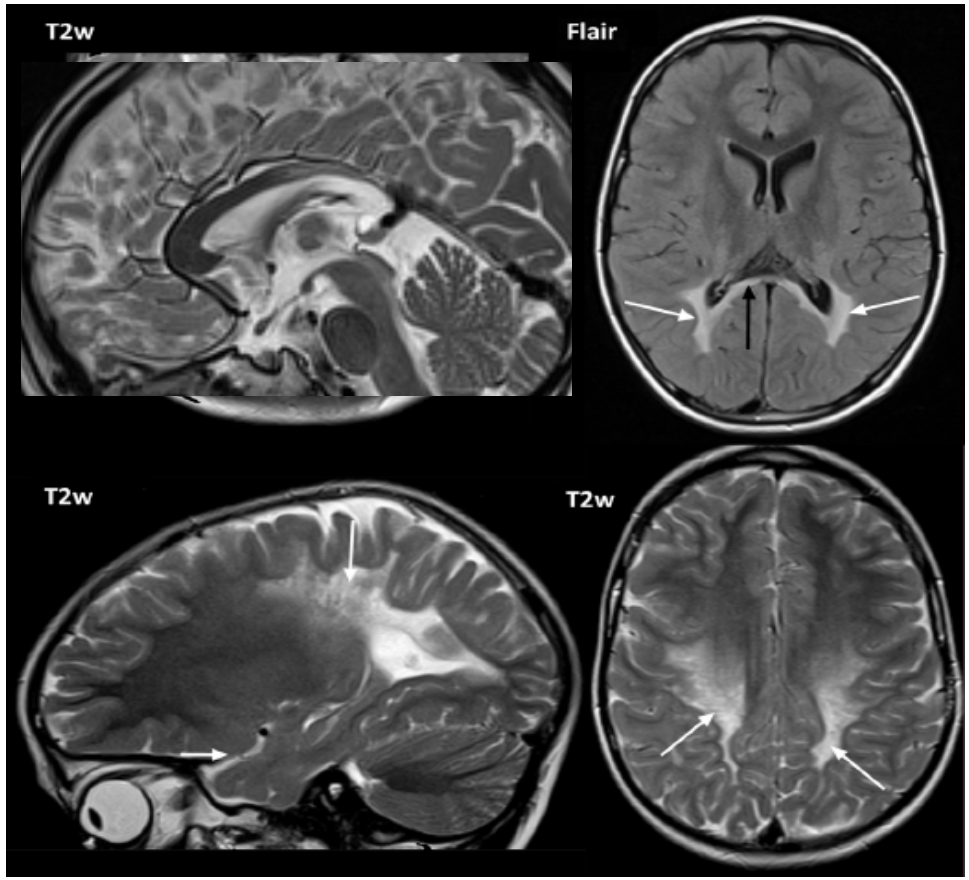


Fig. 4 (See legend on next page)

Bascou et al. A prospective natural history study of Krabbe disease in a patient cohort with onset between 6 months and 3 years of life. Orphanet Journal of Rare Diseases 2018; 13:126

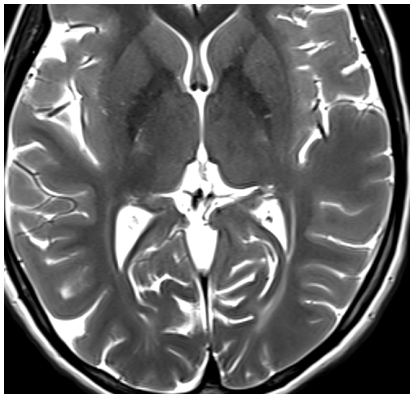
MRI - pattern

later onset



Age at MRI 5 years 1 months, onset 5 years.

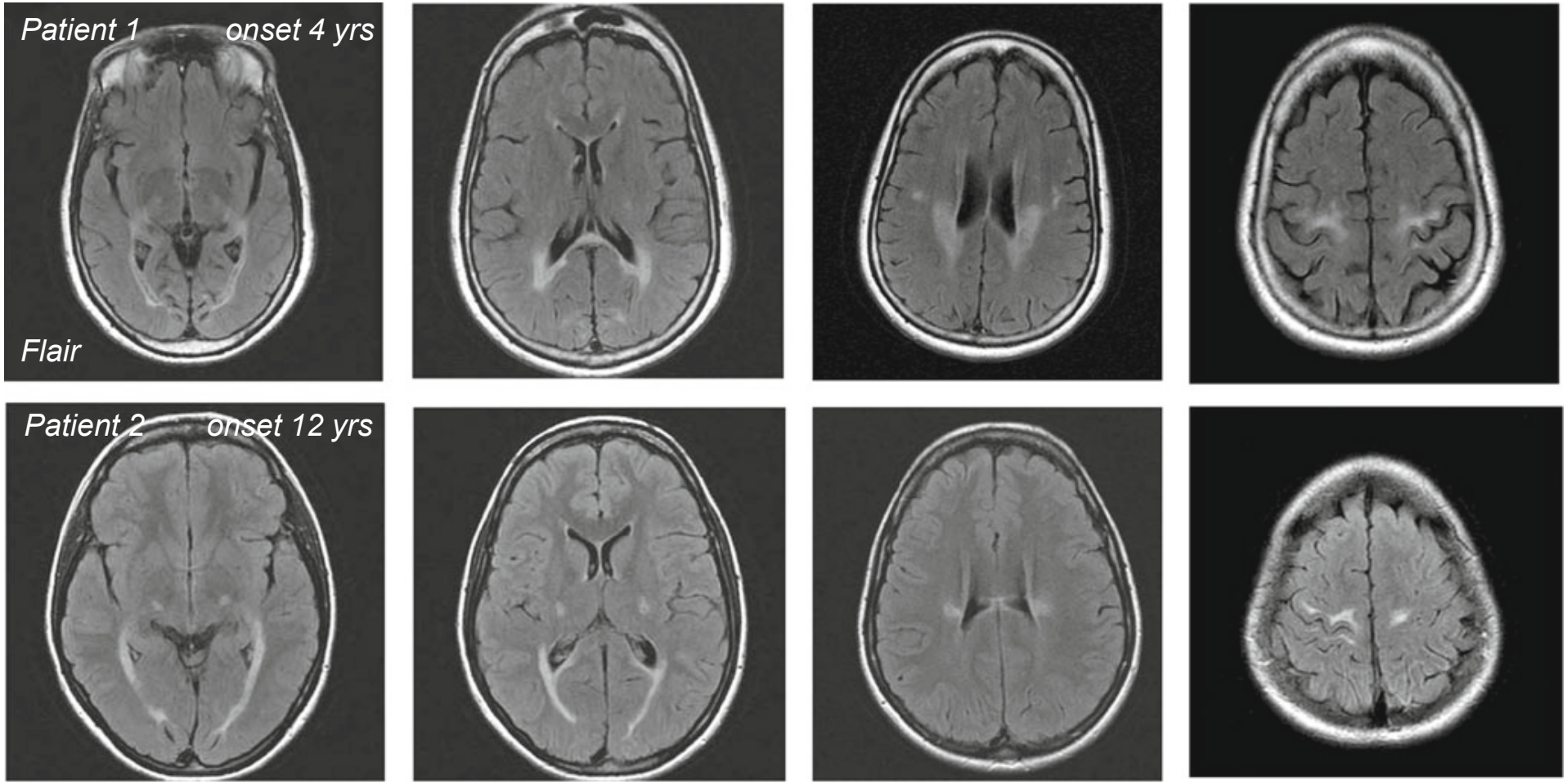
- White matter parieto-occipital
- Corpus callosum (Body and Splenium)
- Pyramidal tract



→Also a late-infantile (onset 10,5 months) and an adolescent patient (onset 12 years) show such a pattern

MRI - pattern

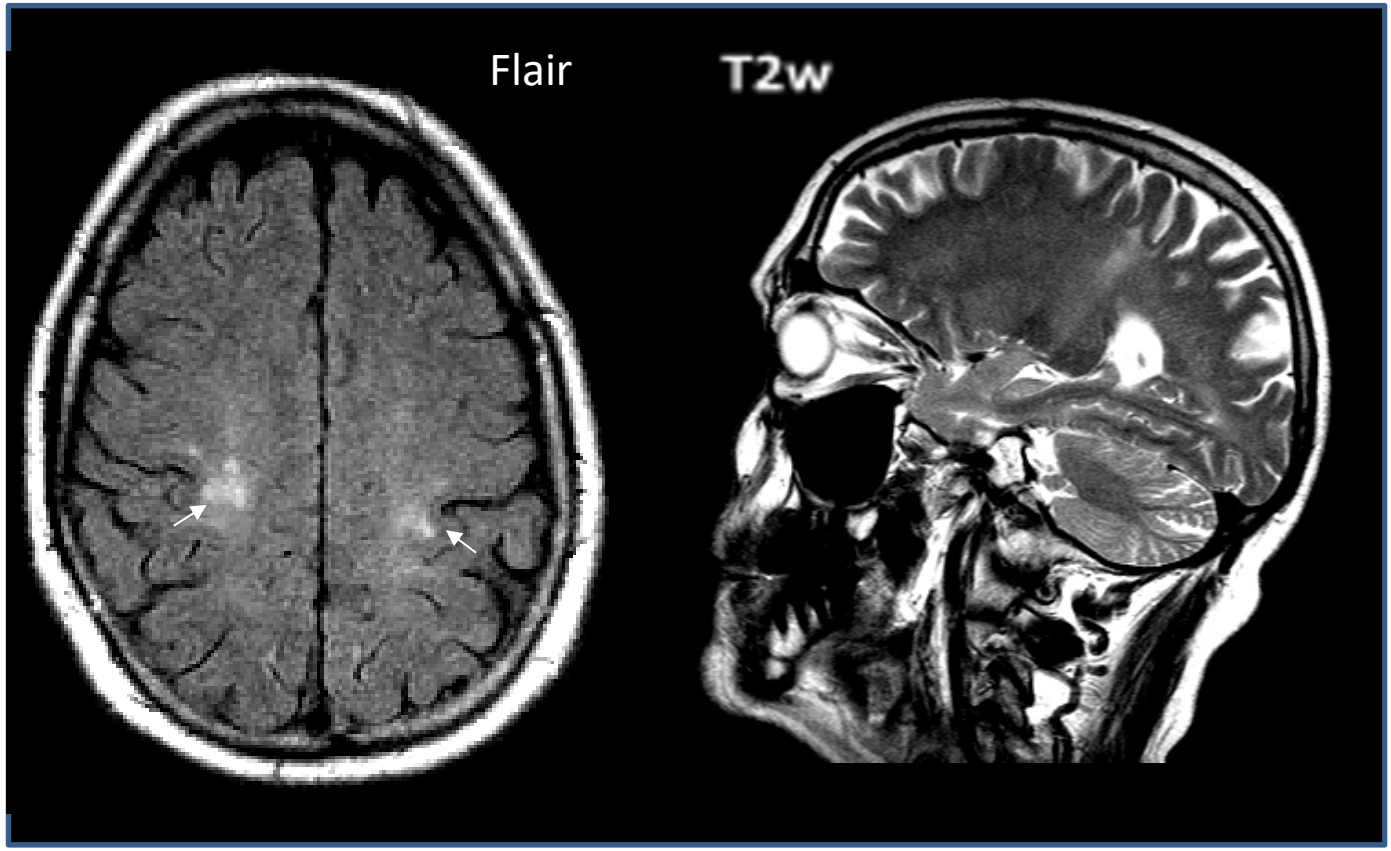
later onset



Debs et al, J Inherit Metab Dis (2013) 36:859–868

MRI - pattern

adolescent, adult



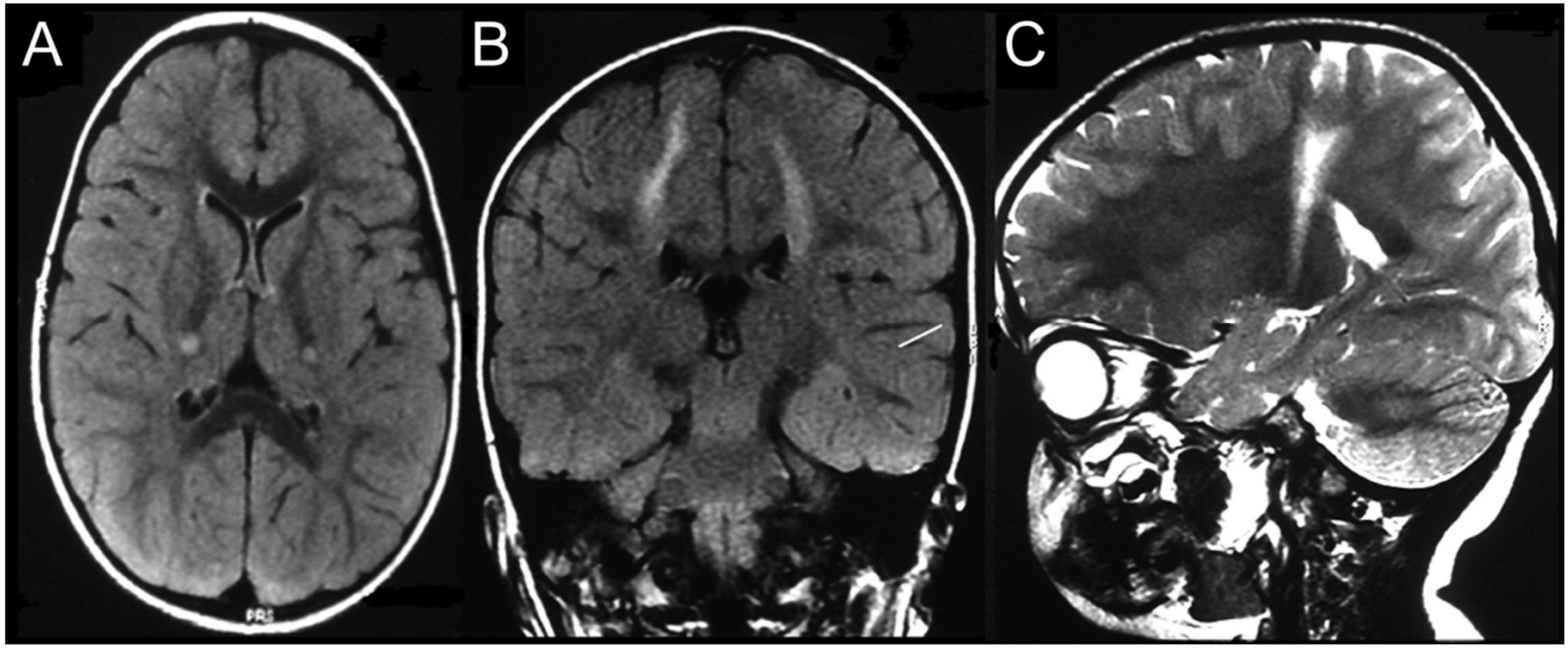
- Pyramidal tract

Age at MRI 70 years, onset 60 years.

MRI - pattern

later onset

Only pyramidal tract involvement

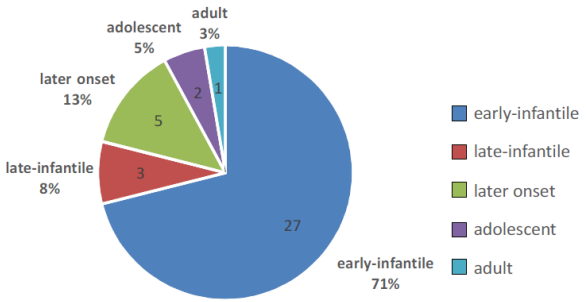


Age at MRI 4 ½ years, onset 4 years.

Shegal et al. Neurology 2011

Summary

clinical characteristics



infantile

early **0 - 6 months**
late 7 - 12 months

irritability, spasticity and neuropathy,
visual loss (optic atrophy)
tube feeding, cognitive decline,
rapid and homogeneous decline

later onset
adolescent and adult

13 months - 10 yrs
adolescent 11 - 20 yrs
adult > 20 yrs

primary motor signs (gait disorder) – PNS+**CNS**
variable course,
especially in adult onset protracted course
cognitive symptoms are later signs

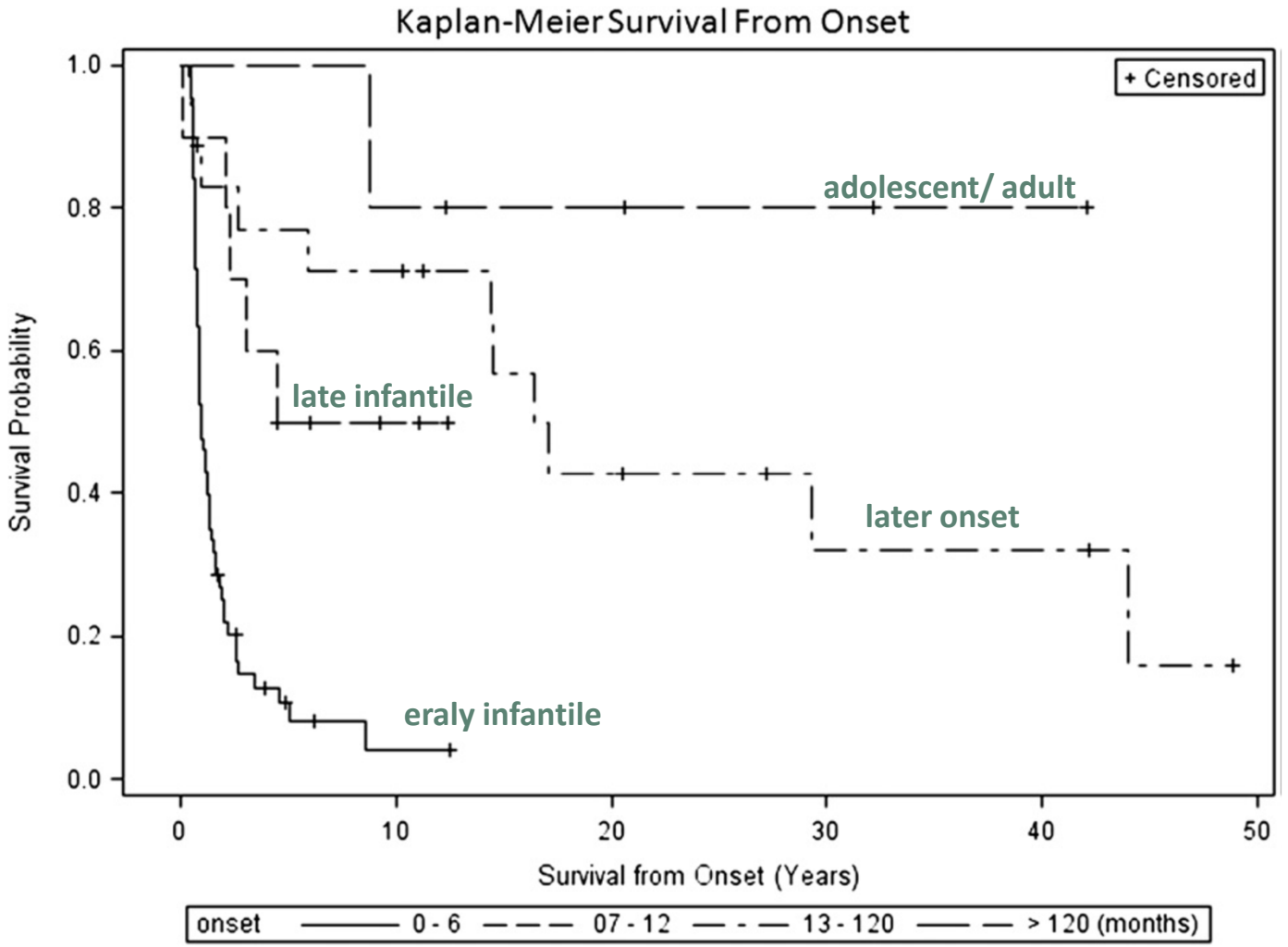
In common

development normal before onset of first symptoms
(only exceptionally early infantile Krabbe may start without clearly first normal development

additional features

neuropathy (nerve conducation velocity ⇓)
CSF protein ⇑

Survival according to onset



From the world-wide registry (Duffner et al, 2012)

Summary

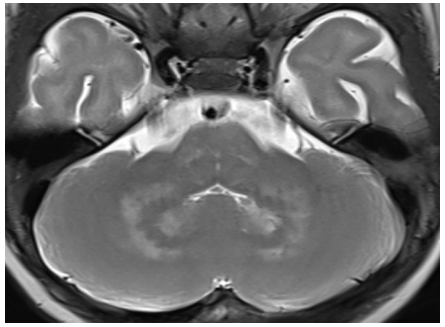
MRI – early signs

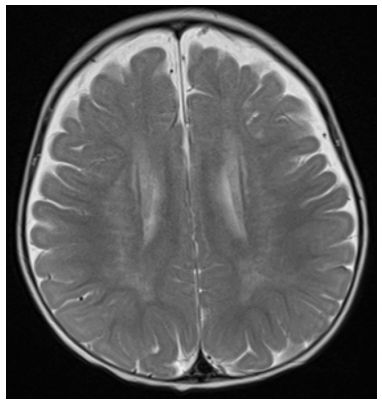
infantile

early	**0 - 6 months**
late	7 - 12 months

central white matter, pyramidal tract

cerebellum: dentate nucleus, cerebellar white matter





later onset

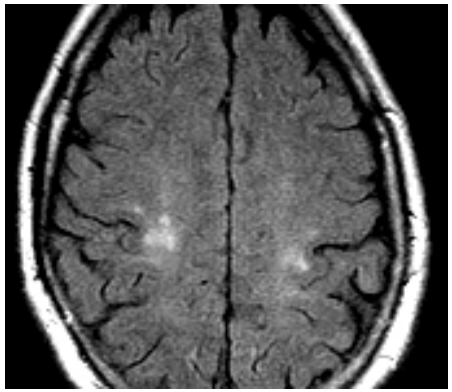
adolescent and adult

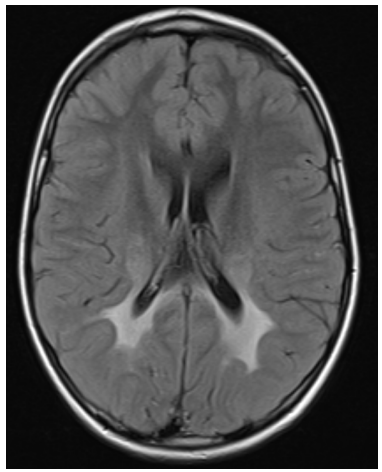
13 months - 10 yrs	
adolescent	11 - 20 yrs
adult	> 20 yrs

peritrogonal white matter,

corpus callosum (splenium)

pyramidal tract





Specific diagnostic procedures

biochemistry

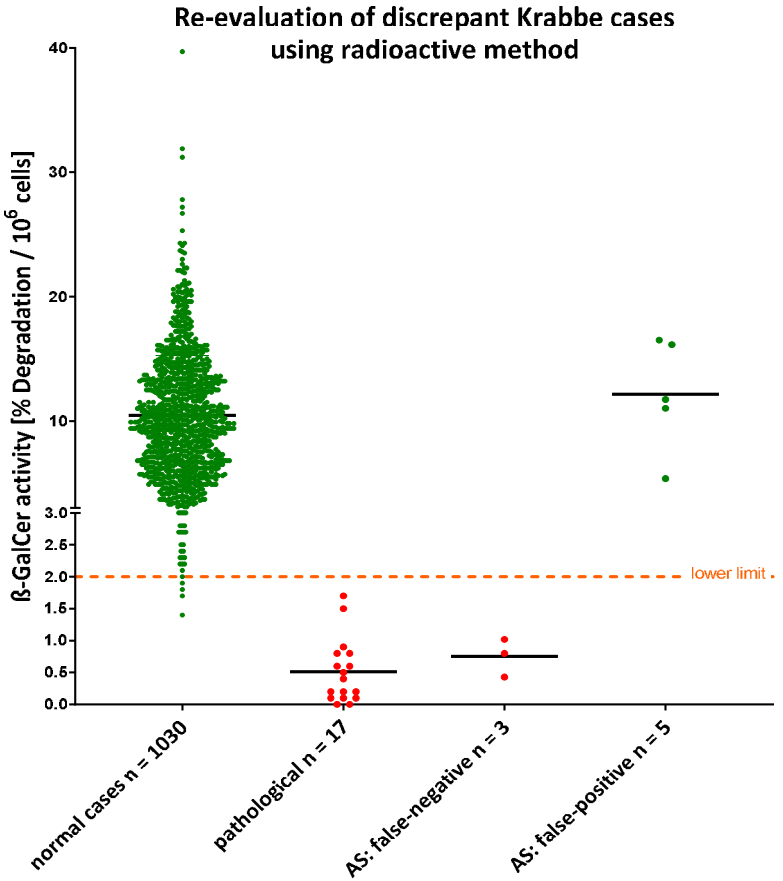
ß-Galactocerebrosidase activity

artificial substrates are preferred due to their technical advantages, their sensitivity and specificity

But they have a risk for false positive or negative results because of the different chemical properties of artificial substrates

When there is a mismatch between clinical, genetic and biochemical findings

⟹ Repeat with an assay based on **radioactive labelled natural substrate**



No correlation with onset of the disease

As also found by others

(*f.ex. Komatsuzaki et al, 2019 Genetics in Medicine)*

Santhanakumaran et al. Poster SSIEM 2022

Specific diagnostic procedures

genetics

Deletions and mutations in the GALC gene

More than 140 different pathogenic variants of the GALC gene

Little genotype-phenotype correlation

- **30 kb deletion** (c.1161 + 6532_polyA+9kbdel)* - infantile onset
- **mutation *c.857G>A*** *(p.Gly286Asp)* – later onset

Prediction difficult because of

- *compound heterocygosity*
- *Other variants not clearly related to course.*

*with about 45 % of the mutated alleles by far the most common mutation in the Caucasian population (here in 4 infantile and 1 later onset patients)

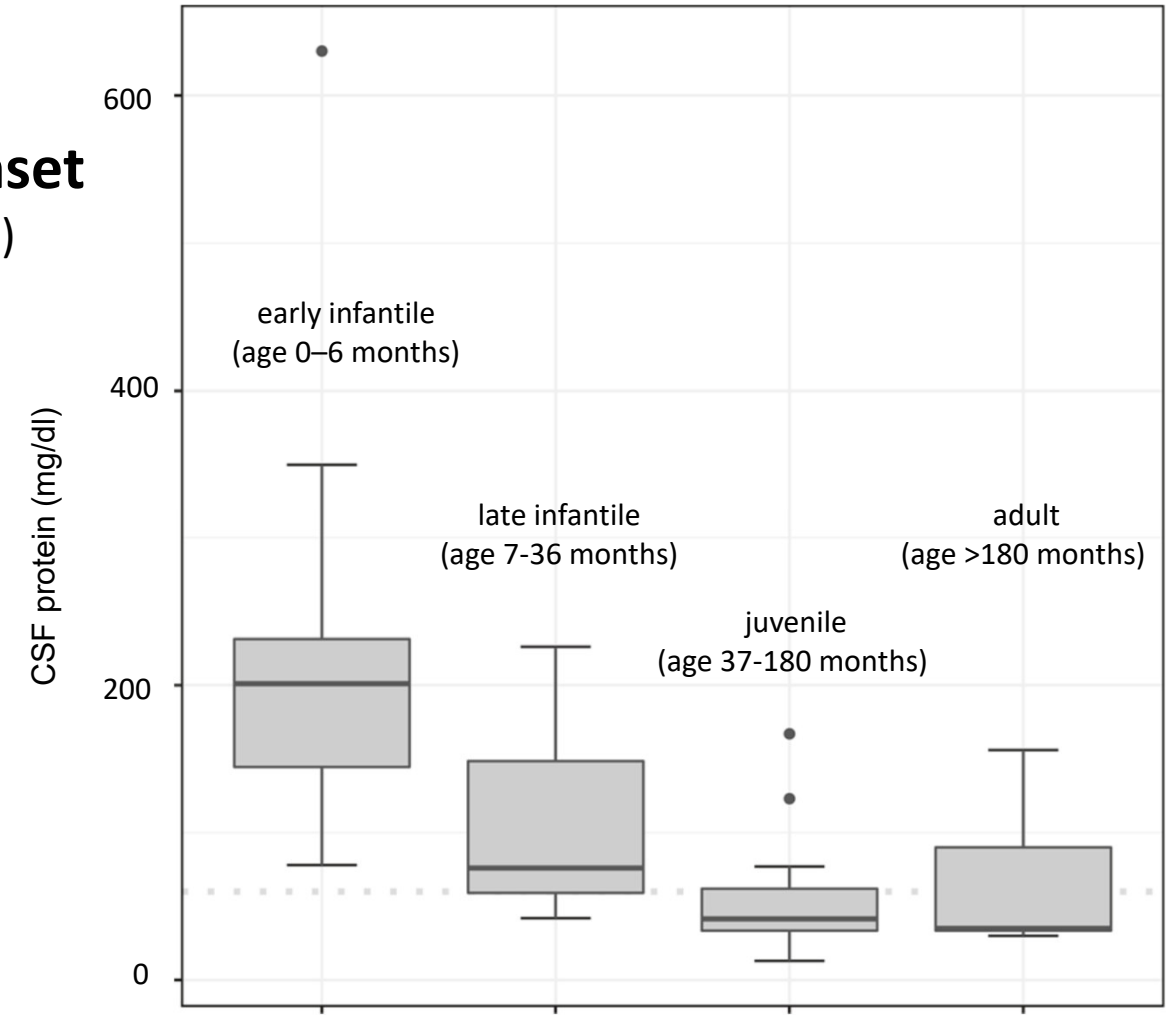
Sakai N, Otomo T.. J Neurosci Res. 2016
Duffner PK, Jalal K, Carter RL Pediatr Neurol. 2009

diagnostic procedures

CSF protein

CSF higher in earlier onset

(data from 248 published cases)



Komatsuzaki et al.. Genetics in Medicine, 2019

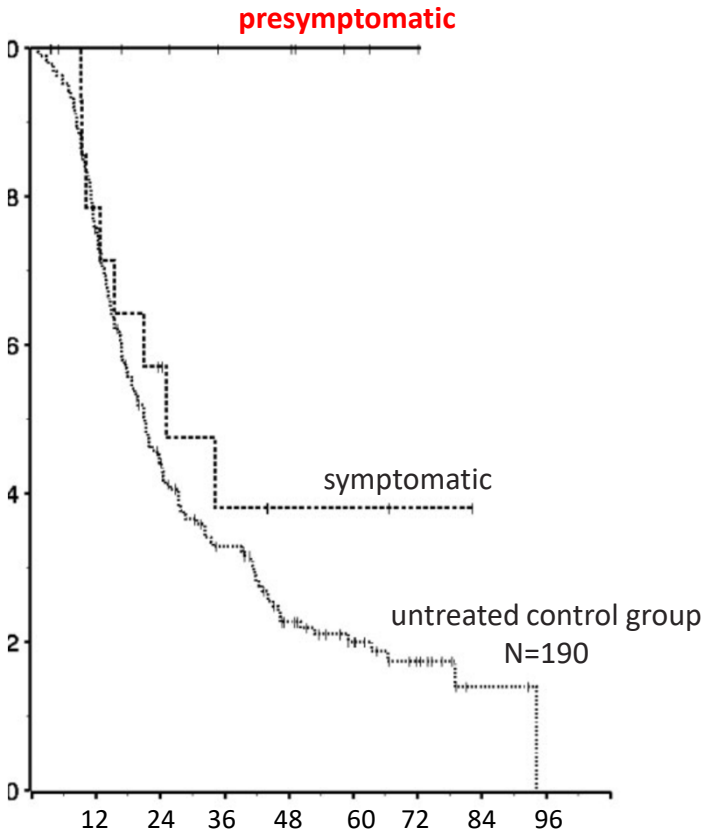
Treatment options

stemcell transplantation

Escolar ML et al. N Engl J Med 2005;352:2069-2081.

Infantile Krabbe
11 asymptomatic newborns
(positive family history)
14 symptomatic infants
(diagnosed between four - nine months of age)

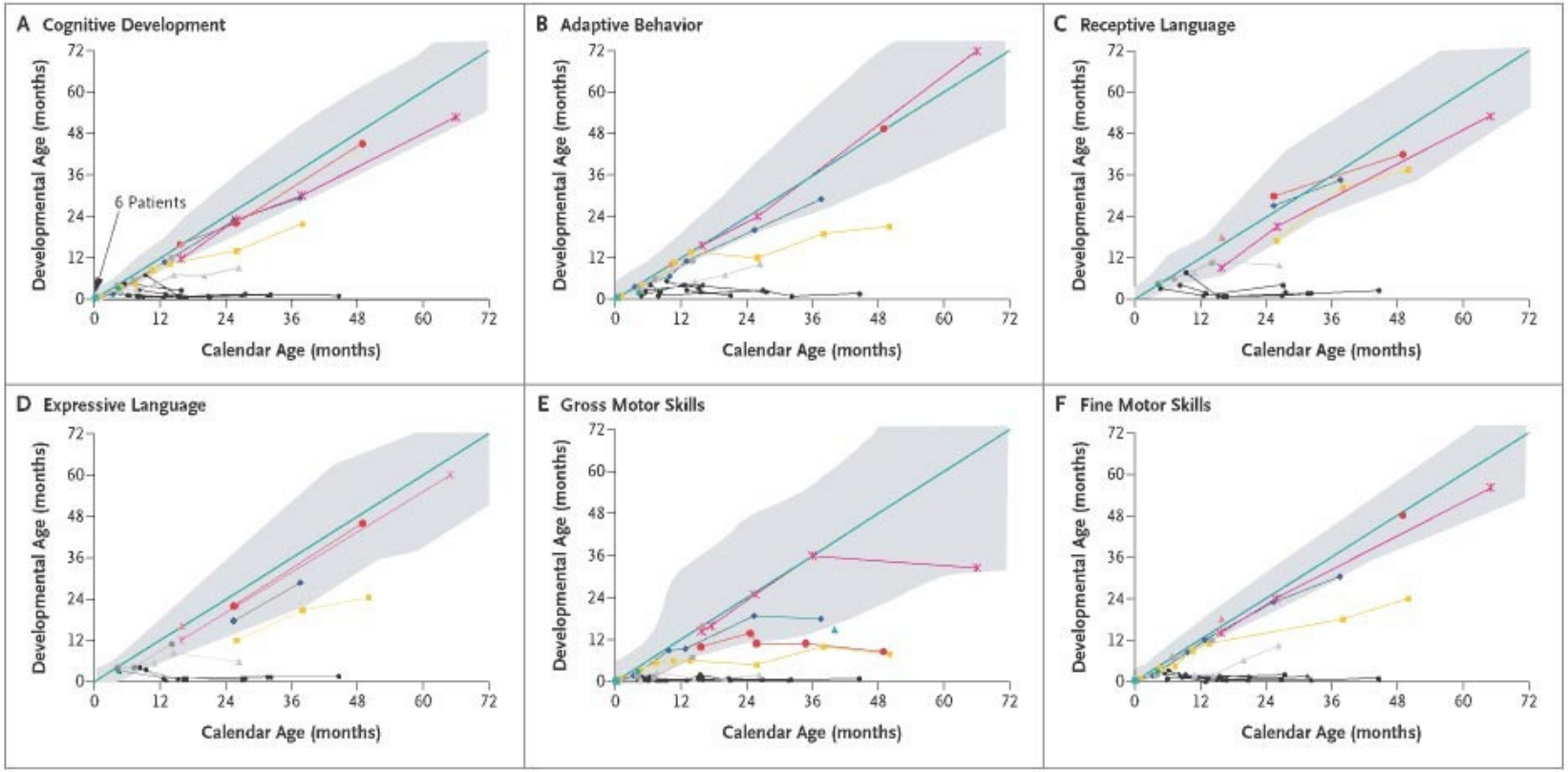
Transplantation of umbilical-cord blood from unrelated donors.



Survival – age (months)

Neurodevelopmental Outcomes

Escolar ML et al. N Engl J Med 2005;352:2069-2081.



Ten of the 11 patients in the newborn group were evaluated after transplantation.

In the symptomatic group, 8 of the 14 patients were evaluated in all domains.

None of the symptomatic patients improved appreciably in any area

Treatment options

stemcell transplantation – early infantile Krabbe

Patients: 18 presymptomatic babies
- detected by **newborn screening** or
- diagnosed prenatally or neonatally because of family history.

Inclusion criteria
(1) diagnosis of early-infantile Krabbe disease established by family history or deficiency of GALC activity in peripheral blood leukocytes and
(2) HSCT within 7 weeks after birth

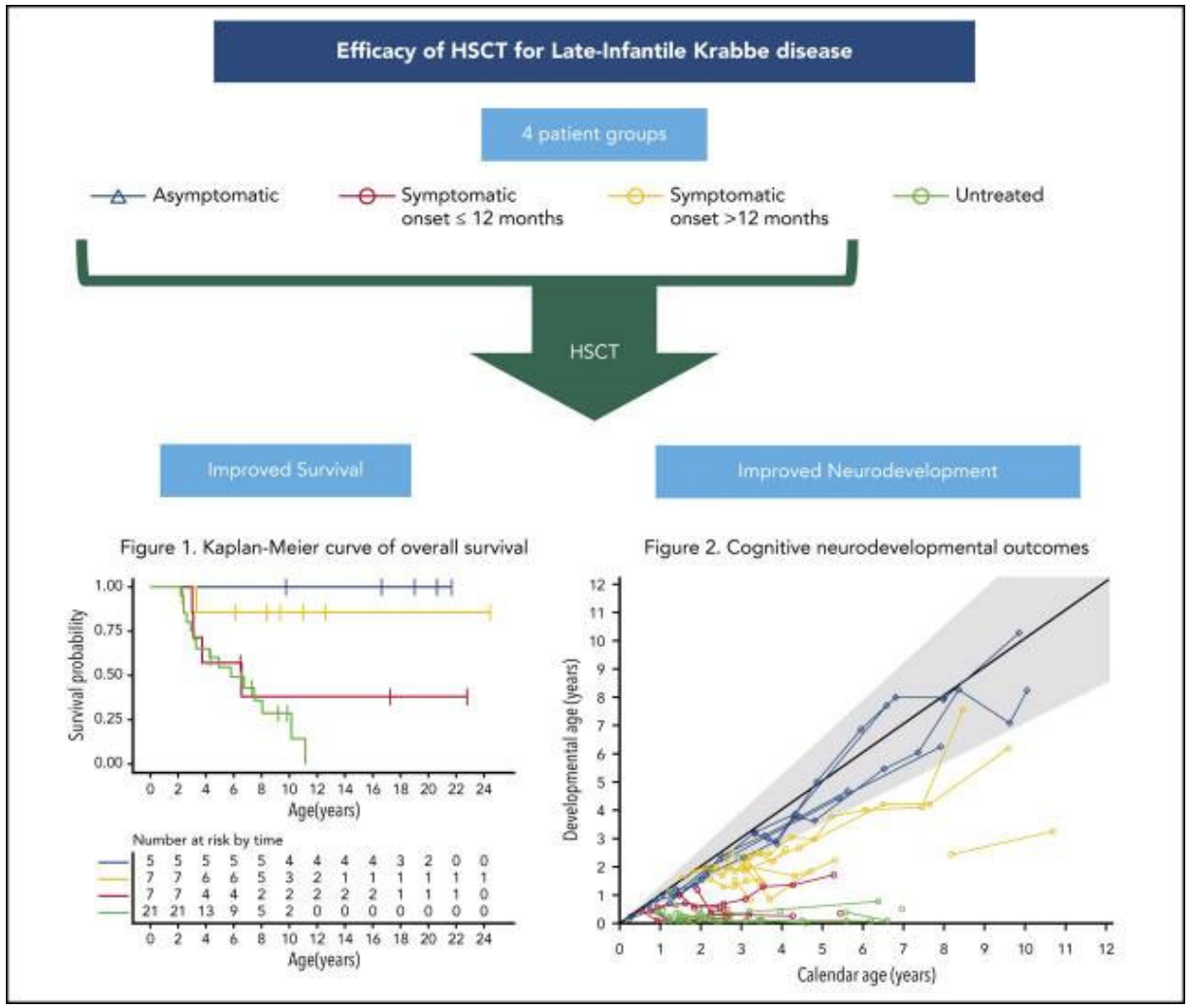
3/18 died from complications related to HSCT
1/18 died from surgical complications (6 yrs)
1/18 died from disease progression

One of the surviving patients has normal cognitive function and 10 continue to develop cognitive skills at a slightly slower rate than normal.

Wright et al. Neurology 2017

Treatment options

stemcell transplantation – Krabbe late infantile and beyond



Yoon et al. Blood 2021

Clinical trials on Krabbe Disease

1. **AAV9-gene therapy** (Passage Bio)
    1. Single application, intracisternal
    2. > 1 months and < 9 months, presymptomatic or early symptomatic < 6 months
    3. Minimum level of neurological development (head lifting, eye tracking, smiling)
    4. 1 EU center (Amsterdam)
    5. Only one patient yet treated in the US

2. **Combination of HSCT and AAV10-gene therapy** (Forge therapeutics)
    1. Intravenous
    2. Phase 1/ 2 clinical study of intravenous gene transfer with an AAV10 vector expressing GALC after HSCT
    3. Infantile KD, 1d to 12 months of age
    4. Eligible for HSCT, reasonable neurological function stabilized after HSCT
    5. US only

Q1 Natural history in Krabbe Disease is characterized by

Correct are three

1. Global developmental delay as first symptoms
2. First development is usually normal
3. Motor signs such as gait disorder are first sings in onset beyond the first year of life
4. Disease course is rapid and homogeneous in the early infantile form
5. In later onset forms age at onset has clearly been shown to predict progression of the disease

Q1 Natural history in Krabbe Disease is characterized by

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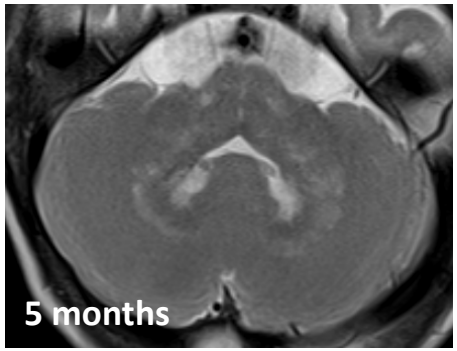
Correct are 2, 3 ,4

Q2 Which MRI is characteristic for Krabbe Disease?

Correct are two

1.



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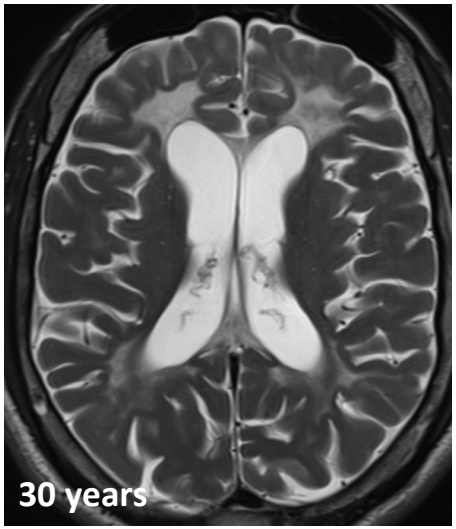

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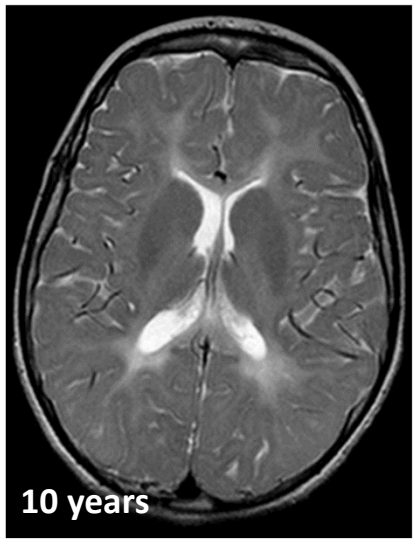
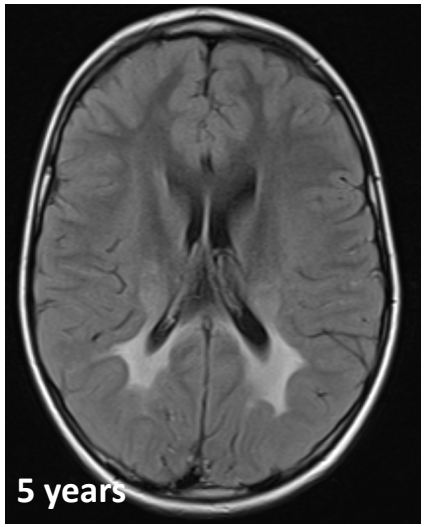


4.



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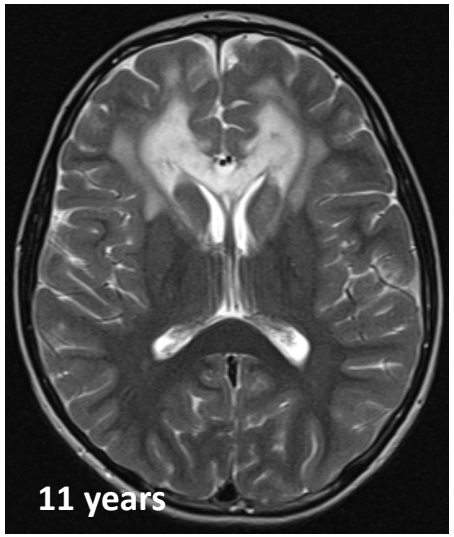

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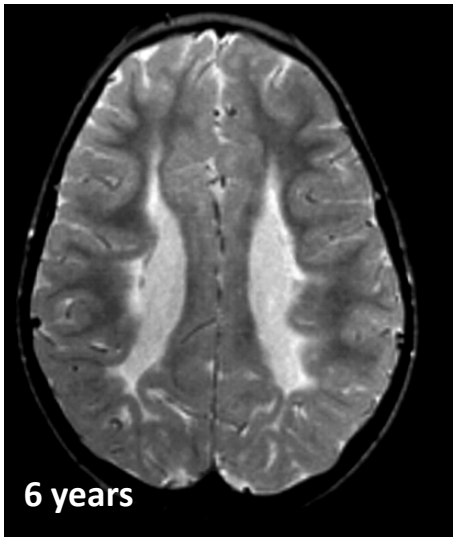
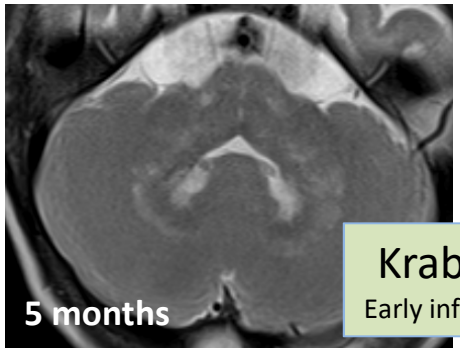


Q2 Which MRI is characteristic for Krabbe Disease?

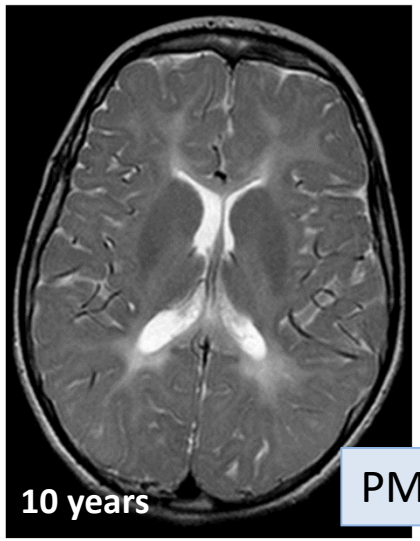
Correct are 1 and 4

1.



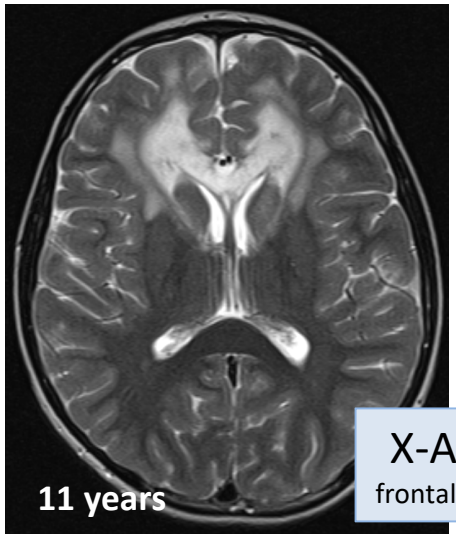
Krabbe
Early infantile

3.



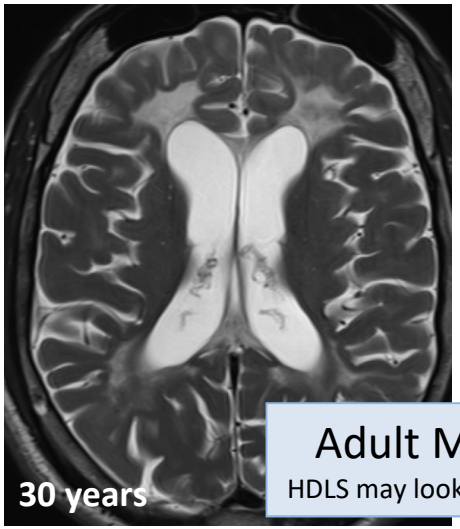
PMD

5.



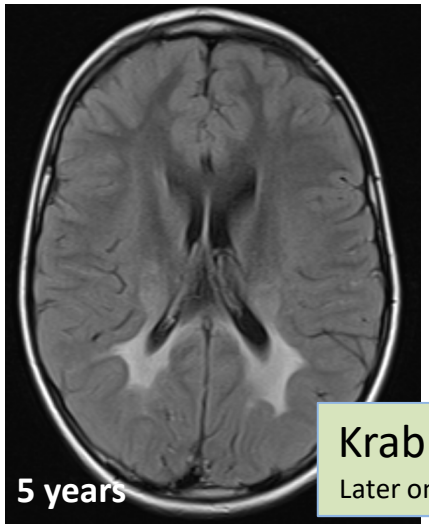
X-ALD
frontal form

2.



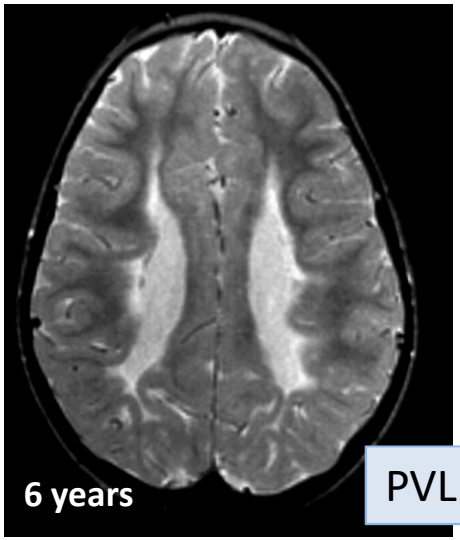
Adult MLD
HDLS may look similar

4.



Krabbe
Later onset

6.



PVL

Q3 Specific diagnostics in Krabbe Disease relies on

Correct are three

1. Deficient ß-Galactocerebrosidase activity
2. Mutations of the ARSA gene
3. Deletions and mutations in the GALC gene
4. Enzyme activity is clearly relate to onset of the disease
5. There is a high genotype-phenotype correlation
6. In unclear cases an assay using radioactive labelled natural substrate is to be preferred

Q3 Specific diagnostics in Krabbe Disease relies on

Correct are 1, 3, 6

1. Deficient ß-Galactocerebrosidase activity
2. Mutations of the ARSA gene
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4. Enzyme activity is clearly relate to onset of the disease
5. There is a high genotype-phenotype correlation
6. In unclear cases an assay using radioactive labelled natural substrate is to be preferred

Key conclusions

- Different forms of disease with different clinical courses and MRI patterns – infantile, especially early infantile, Krabbe is the most frequent form, later onset forms are different with respect to first signs, dynamics and imaging

- Diagnostic procedures
  → enzyme measurement (cave pitfalls, when using artificial substrate)
  → genotype (little phenotype correlation)

- (New) treatment options
  → stemcell transplantation (presymptomatic infantile, early symptomatic later onset)
  → gene therapy trials

European Reference Network for rare or low prevalence complex diseases

Network Neurological Diseases (ERN-RND)

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European Reference Network for rare or low prevalence complex diseases

Network Neuromuscular Diseases (ERN EURO-NMD)

NEXT Webinar

‘DBS in Dystonia – Targets, programming and therapeutic challenges’

by Philipp Capetian,

University Hospital Würzburg, Germany

18. October 2022