HEIDELBERG UNIVERSITY HOSPITAL

Management of glutaric aciduria type 1 after 6 years of age

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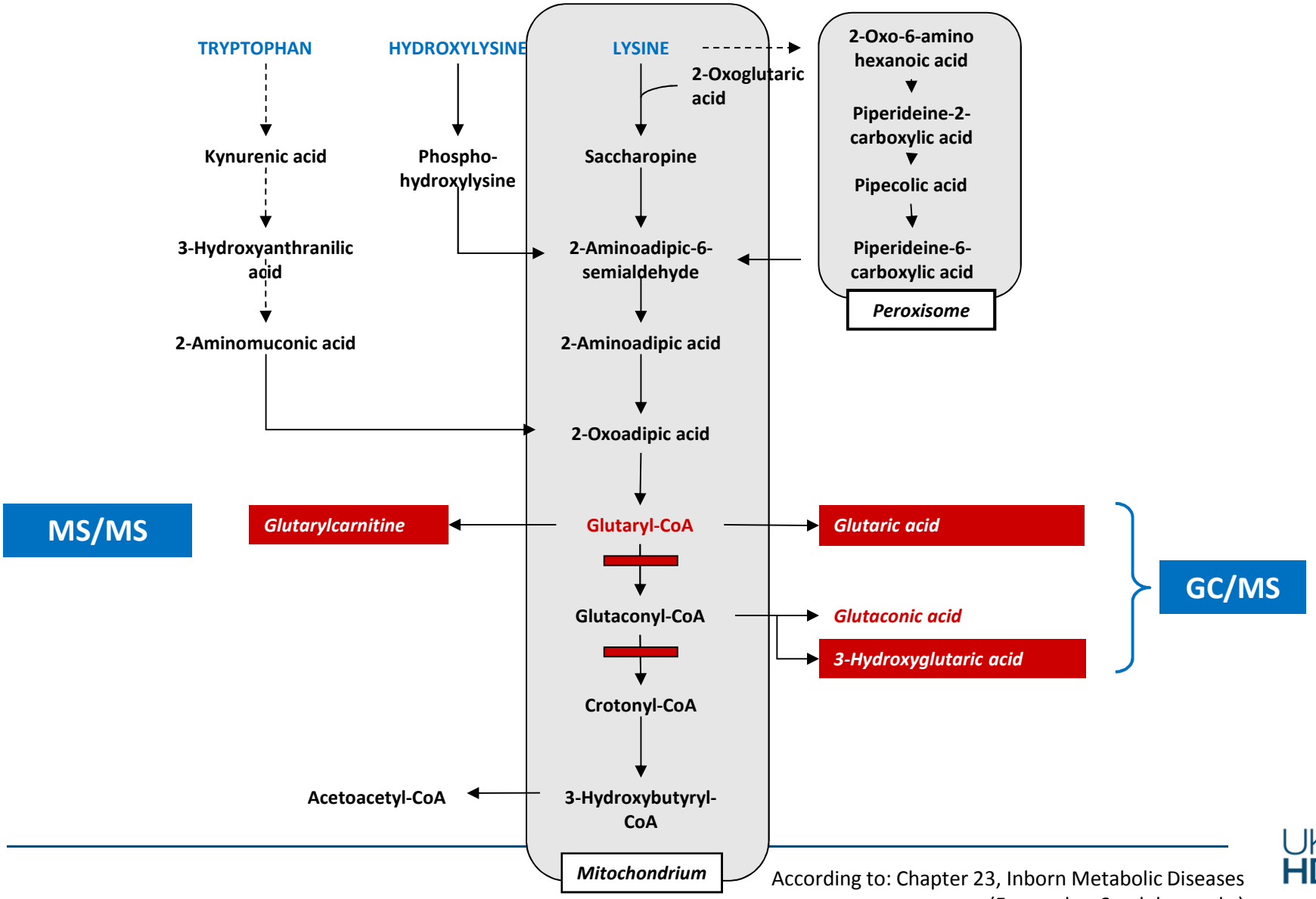
UK HD

Conflict of interests

- None

INTRODUCTION

Degradative pathways of lysine, hydroxylysine and tryptophan



According to: Chapter 23, Inborn Metabolic Diseases (Fernandez, Saudubray eds,)

Glutaric aciduria type 1 (GA1)

Change of the disease course

1995

today

Forms of neurologic disease in GA1

- ***Striatal* injury**, i.e. dystonic movement disorder
  - 0-6 years (‚*window of vulnerability*‘)
  - ***Acute*** vs. ***Insidious*** onset
  - Irreversible
  - **Strong** preventive effect of treatment

- ***Extrastriatal* abnormalities,** clinical relevance unknown
  - Frontotemproal hypoplasia, white matter abnormalities, delayed myelination, T2-hyperintensity in Globus pallidus, Thalamus, Substantia nigra or Nucleus dentatus
  - In (un-)treated patients < and > 6 years; even prenatally
  - Regression and progression, highly dynamic

Variants of striatal injury < 6 years

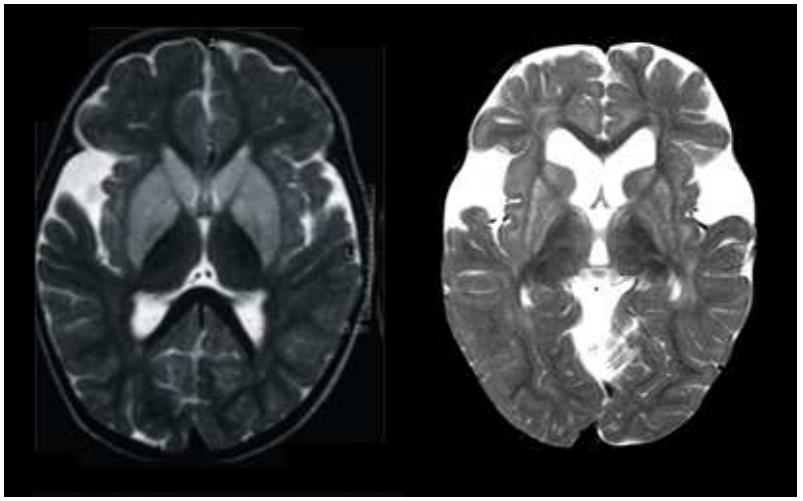
***Acute* onset (encephalopathic crises)**

(if untreated): 50-70%, mostly 3-24 months

⇨ **Triggers: Catabolism**

(infectious diseases, vaccinations, surgery)

Extensive striatal lesions, mostly severe dystonia



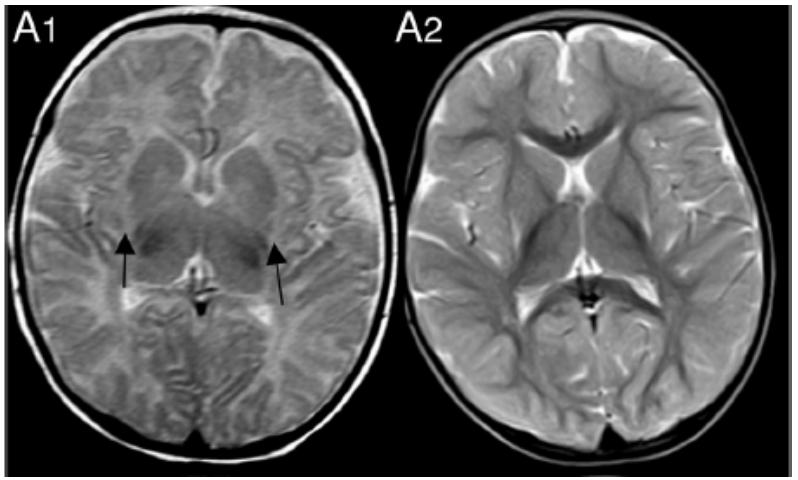
***Insidious* onset** : 15-30%, 12-72 months

⇨ **Triggers: deviations from dietary treatment**

Lesions restricted to dorsolateral putamen

Mild – moderate dystonia

Asymptomatic latency phase despite existing lesions

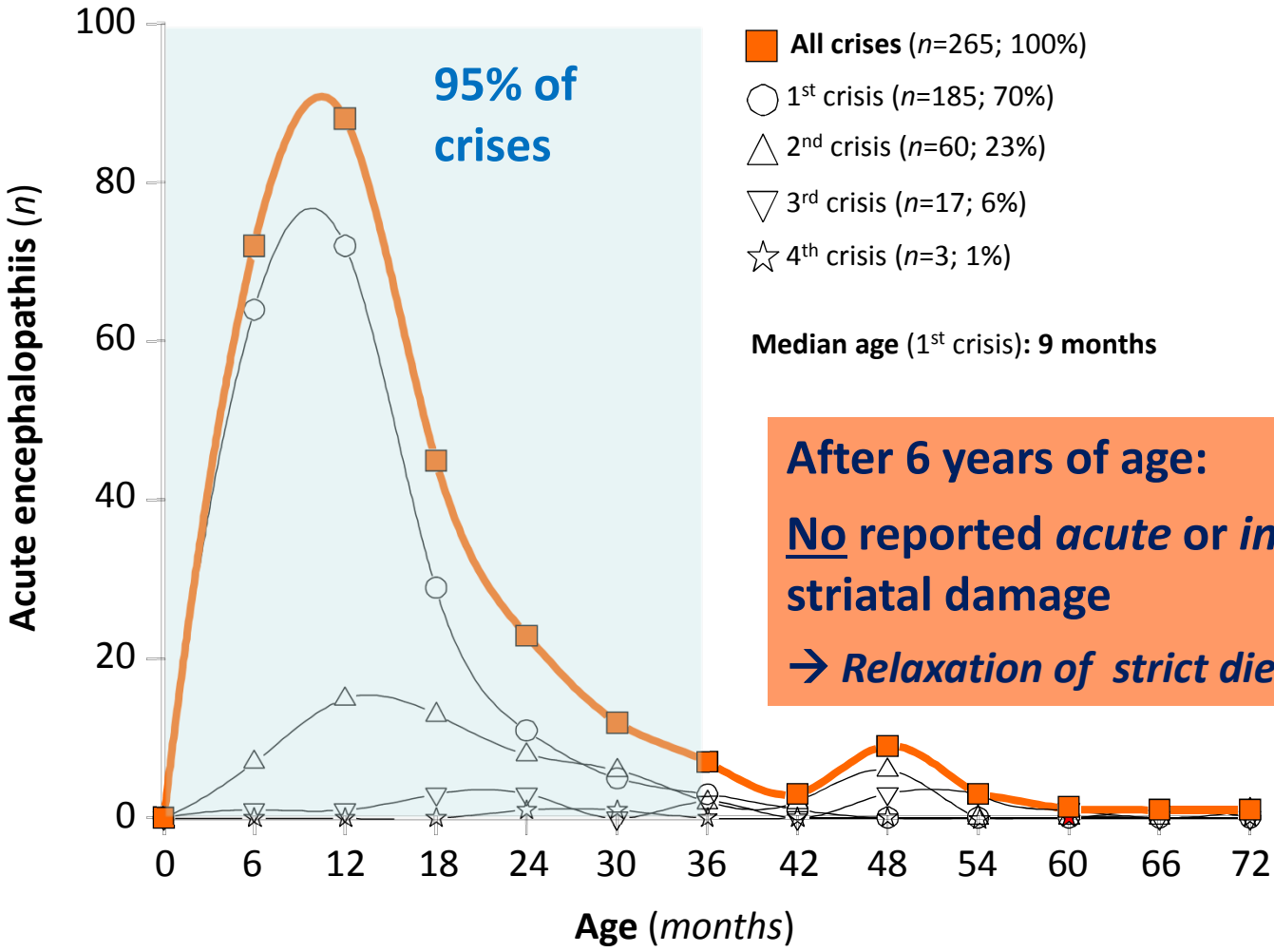


Heringer et al. *Ann Neurol* 2010; 68: 742-52
Harting et al. *Brain* 2009; 132: 1764-1782

Boy et al. *J Inherit Metab Dis* 2018, [Epub ahead of print]

Acute encephalopathic crises occur from 0-6 yrs

'Window of vulnerability'



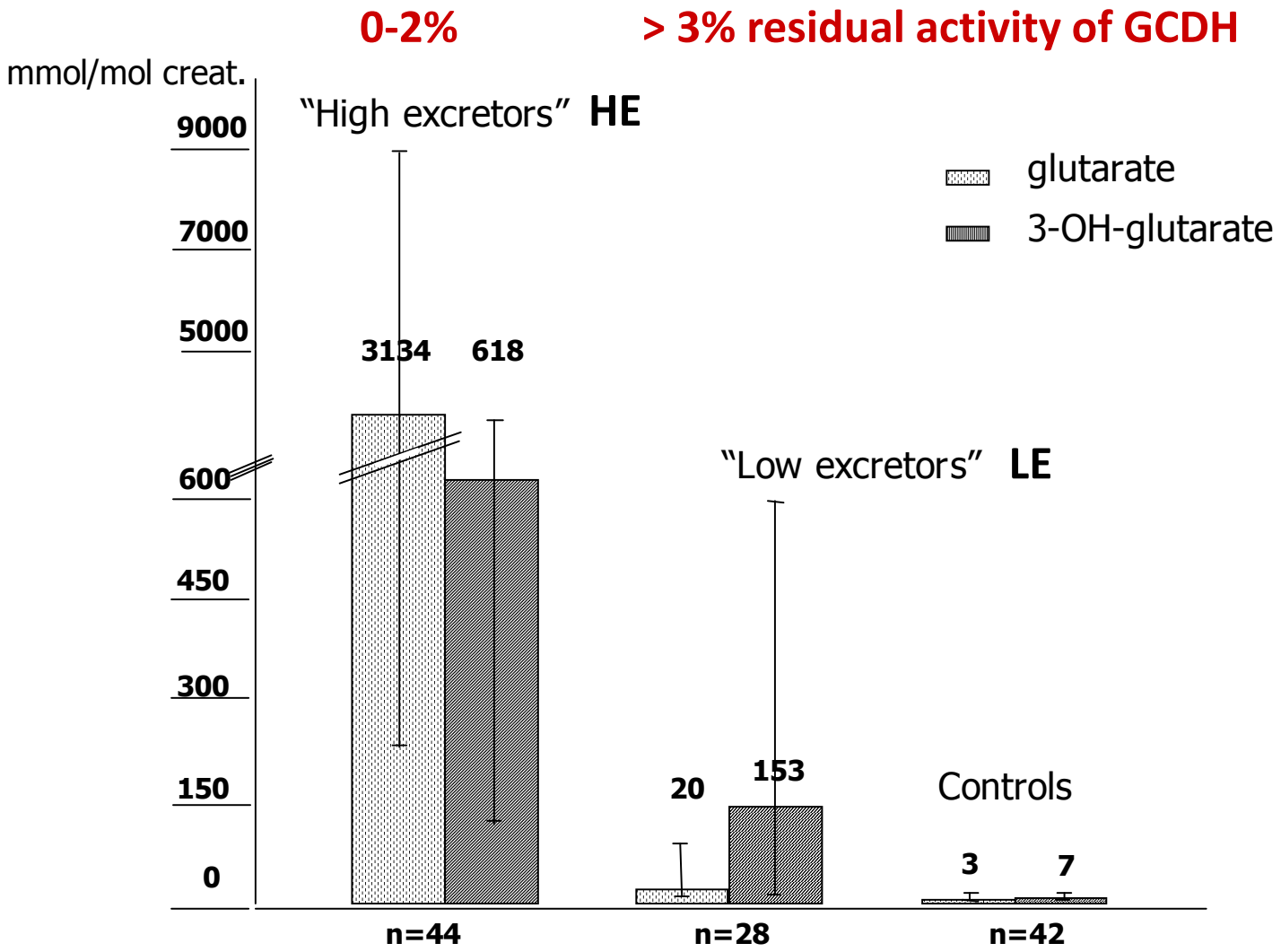
After 6 years of age:

No reported *acute* or *insidious* onset striatal damage

→ *Relaxation of strict dietary treatment*

Kölker et al. *Pediatr Res* 2006; 59(6):840-7

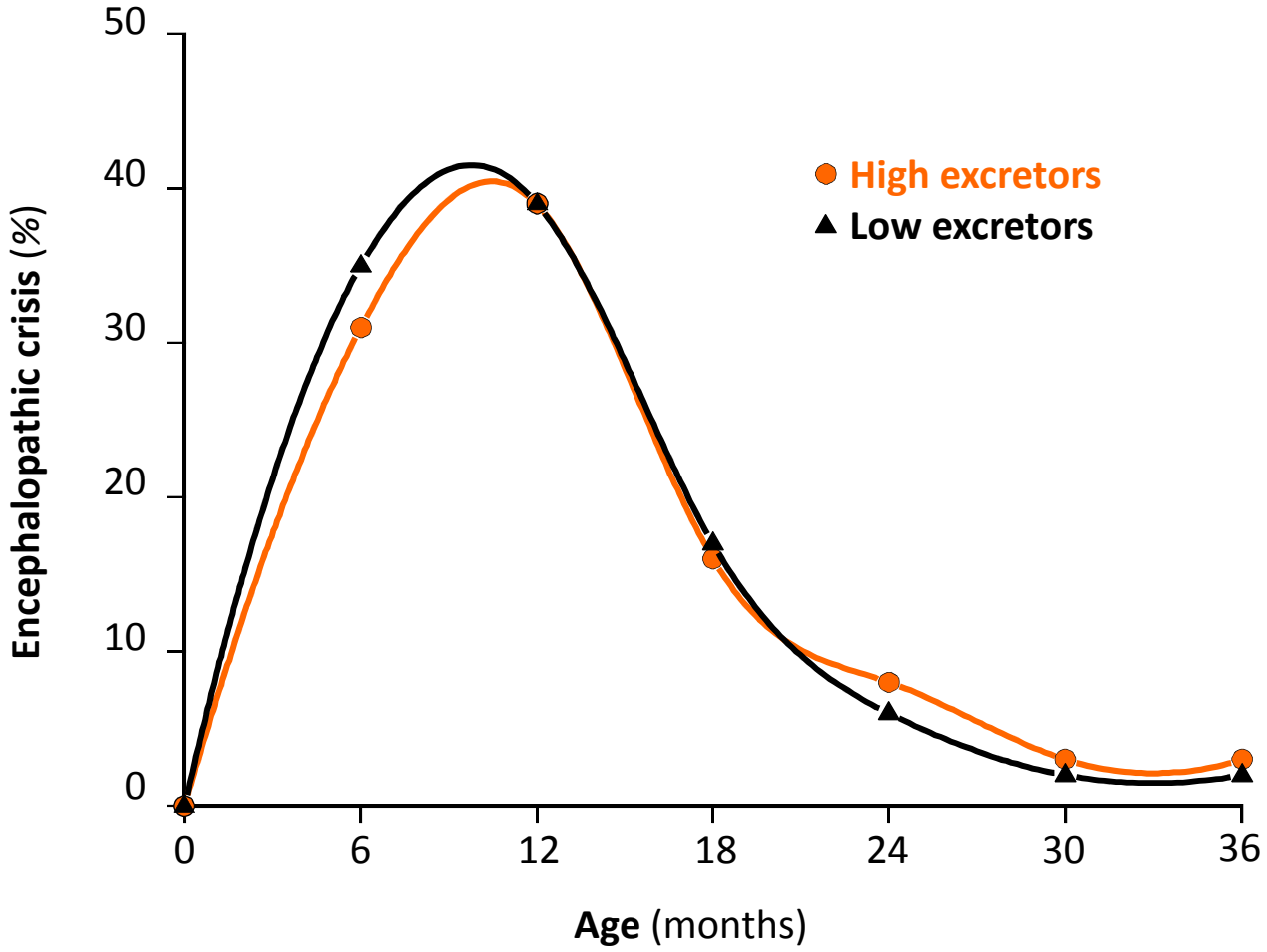
Biochemical phenotypes (urine, plasma)



Christensen et al. *J Inherit Metab Dis*. 2004;27: 861-8.
Baric et al. *J Inherit Metab Dis.* 1999;22: 867-81.

No apparent correlation?

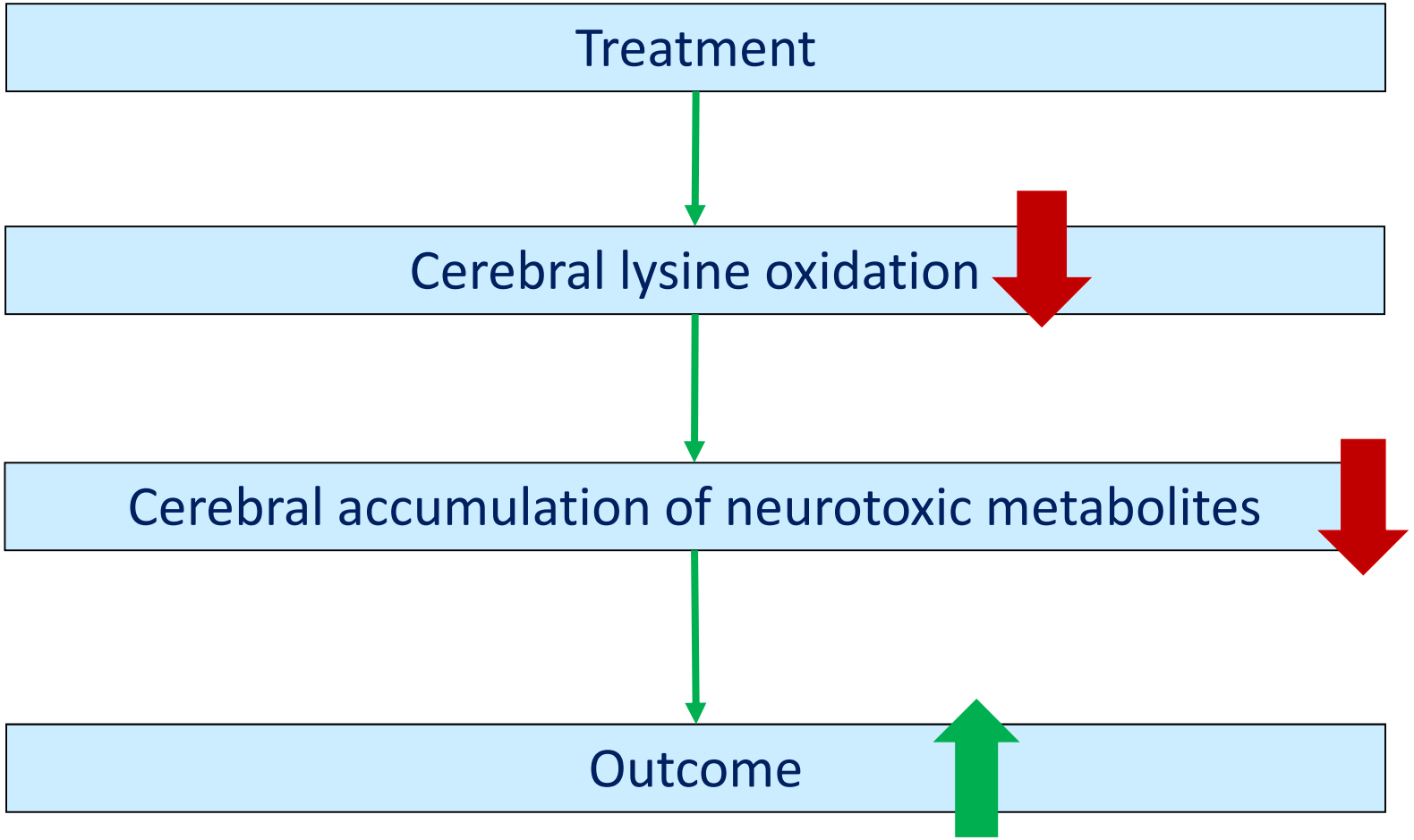
Biochemical and clinical phenotype



Kölker et al. *Pediatr Res* 2006; 59:840-7

TREATMENT

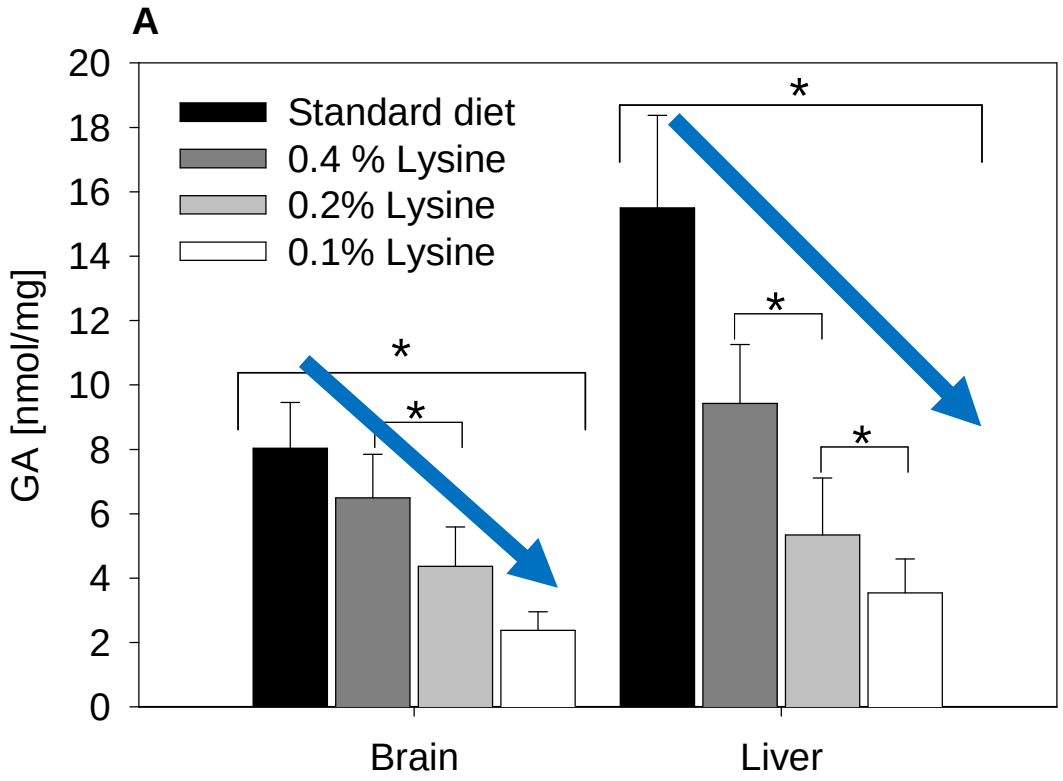
Treatment strategy



Low lysine diet – *Proof of principle*

Gcdh$^{-/-}$ mice

Reduction of cerebral accumulation of neurotoxic metabolites



0,4 and 0,2% lysine: **adequate growth**

0,1% lysine: inadequate growth

Sauer et al. *Brain* 2011; 134:157-70.

Treatment recommendations < 6 years

according to the current guideline

Maintenance treatment

- **Low lysine diet**
- **Lysine-free amino acid mixture**
- **Carnitine supplementation**

	Recommendation 5
Strong recommendation for	Low-lysine diet with additional administration of lysine-free, tryptophan-reduced AAMs containing essential amino acids is strongly recommended for dietary treatment up to age 6 years.
Level of evidence	High to moderate (SIGN level 2++ to 4). Consistency of evidence is high.
Clinical relevance	High.

Emergency treatment (transiently)

→ *Prevention of increased lysine oxidation*

Revised Guidelines: since 2007, 1st revision 2011, 2nd revision 2017

Boy et al. *J Inherit Metab Dis.* 2017; 40: 75-101.

Treatment recommendations < 6 years

according to the current guideline

Table 2 Metabolic maintenance treatment

Treatment		Age				
		0–6 months	7–12 months	1–3 years	4–6 years	>6 years
1. Low-lysine diet						
Lysine (from natural protein)[a]	mg/kg per day	100	90	80–60	60–50	Controlled protein intake using natural protein with a low-lysine content and avoiding lysine-rich food; e.g., according to national recommendations such as Optimix[d]
Amino acid mixtures (protein)[b]	g/kg per day	1.3–0.8	1.0–0.8	0.8	0.8	
Energy	kcal/kg per day	100–80	80	94–81	86–63	
2. Micronutrients[c]	%	≥100	≥100	≥100	≥100	≥100
3. Carnitine	mg/kg per day	100	100	100	100–50	50–30

[a] Lysine/protein ratios vary considerably in natural food, and thus, natural protein intake in children on a low-lysine diet is dependent on the natural protein source. Natural protein intake is relatively high if patients predominantly use natural protein with a low-lysine content. For this reason, numerical data on natural protein are not provided

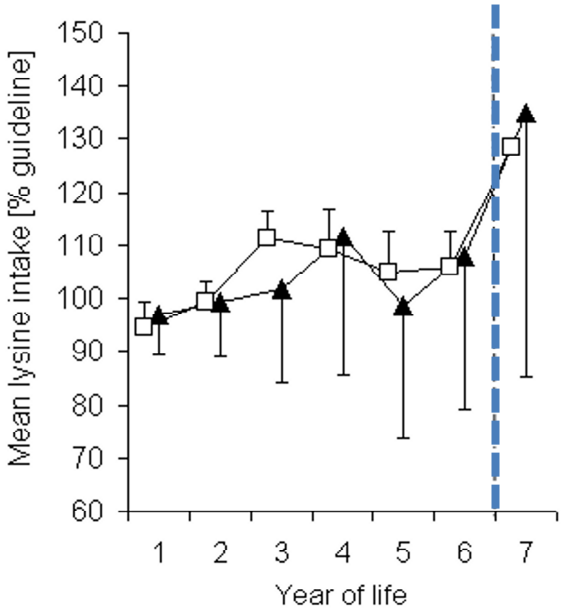
[b] Lysine-free, tryptophan-reduced amino acid mixtures should be supplemented with minerals and micronutrients as required to maintain normal levels. Adequate intake of essential amino acids is provided from natural protein and lysine-free, tryptophan-reduced, amino acid supplements. The amount of amino acid supplements is adjusted to reach at least the safe levels (Dewey et al. 1996)

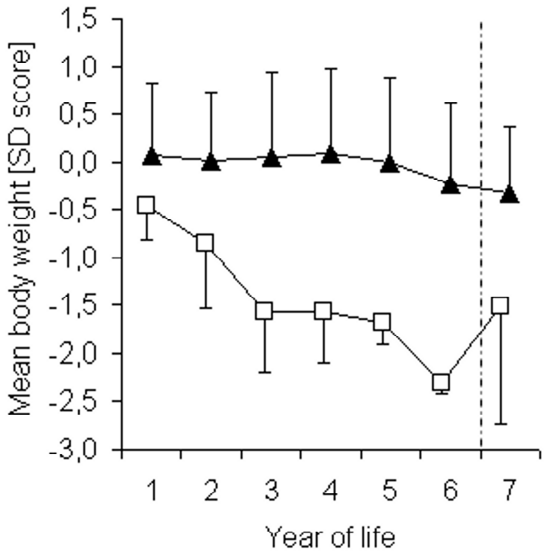
[c] According to international dietary recommendations (D-A-CH 2015)

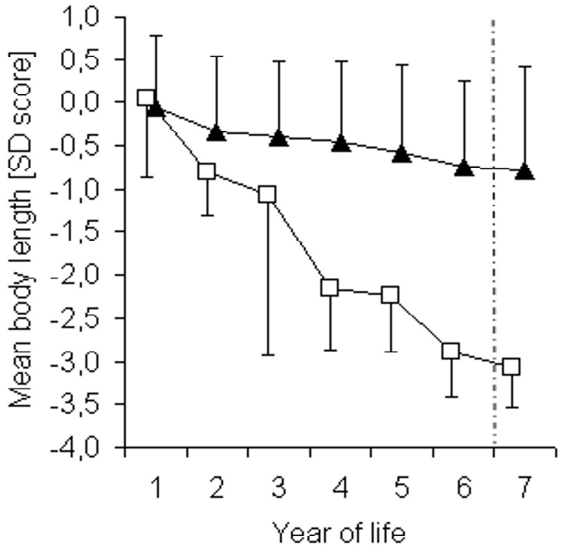
[d] Optimix®, National Nutritional Recommendations for Children and Adolescents, by Research Institute for Child Nutrition Dortmund, Germany; URL: http://www.fke-do.de/index.php

Boy et al. *J Inherit Metab Dis.* 2017; 40: 75-101.

Safety of dietary treatment







Lysine intake | **Body wheight** | **Body length**

▲ **Asymptomatic (n=29)**

□ **Dystonia (n=4)**

Boy et al. 2013, *J Inherit Metab Dis*; 36:525-33

Treatment recommendations > 6 years

according to the current guideline

- *Controlled protein intake **using natural protein with a low lysine content** and **avoiding lysine-rich food** is advisable after age 6 years*

	Recommendation no. 6
Recommendation for	After age 6 years, dietary treatment should follow an age-adapted, protein-controlled protocol based on safe levels for protein intake. Dietary changes should be accompanied by regular dietary advice.
Level of evidence	Moderate (SIGN level 2+ to 4). Consistency of evidence is high.
Clinical relevance	High.

SIGN Scottish Intercollegiate Guidelines Network

Boy et al. *J Inherit Metab Dis.* 2017; 40: 75-101.

Dietary principles > 6 years

- The *strict* diet with calculation of lysine intake and supplementation of a lysine-free amino acid mixture **can be relaxed > age 6 years** to **protein controlled nutrition**, i.e. lysine intake ↑
- Controlled protein nutrition is based on national recommendations for healthy child nutrition, e.g. the *Optimix* concept *(optimized mixed food),* formulated by the *Research Institute of Child Nutrition, Germany*
- **Basic food > 6 years is cereals and cereal products, fruits and vegetables** (low-lysine containing or lysine-free food)
- This needs to be supplemented with **limited amounts of animal food products** to **maintain sufficient intake of energy, micronutrients and vitamins** (i.e. food that has not been used < 6 years)
- Amino acid mixture is then no longer necessary
- Larger amounts of food with high lysine content should be avoided

The ‚lysine traffic light‘

protein controlled diet

Appropriate (=basic) Food (low lysine or lysine –free)	Limited Food	Unappropriate Food
• **Cereal** *Bread, Pasta, Rice, pastries (without nuts or seed)* • **Potatoes** • **Vegetables** (without pulse) • **Fruits** • **Coconut, Macadamia nuts, walnuts, hazelnuts, pecans, chestnuts** • **Cream, Creme fraiche** *Butter, margarine, vegetable oil, lard* • **Sugar and sugar-containing food** *jam, jelly, honey, sirup, sweets, chocolate*	• **Milk and milk products** *yogurt, cheese with >30% fat* • **Eggs** • **Meat, sausages** • **Fish** • **Pulse** (100-150 g boiled per week) • **Nuts and seed** *almonds, brazil nuts, pine nuts, sesame, linseed* ***Milk and milk products should be preferred to meat and sausages*** *According to Optimix*	• **Nuts and seeds > 1000 mg lysine/100g** *Peanuts, Cashew nuts, pistachio, pumpkin seed, sunflower seed, poppy seed* • **Fish , meat, sausages** *bigger portions* • **Pulse** *Bigger portions of lentils, thick beans, soya beans, peas , chickpeas*
Can be used without limitation	**Necessary for adequate intake of high quality protein, micronutrients and vitamins**	**Should be avoided**

Protein controlled nutrition

according to Optimix® ('optimized mixed food') recommendations for school children and adolescents, formulated by the Research Institute of Child Nutrition, Germany

E.g. recommendations for average intake of animal food products

Age (years)

Animal food product	Recommended intake	6	7 - 9	10 - 12	13 - 14	15 - 18
Milk, Milk products*	*ml/day* *g/day*	350	400	420	425 (f) 450 (m)	450 (f) 500 (m)
Meat, Sausage	*g/day*	40	50	60	65 (f) 75 (m)	75 (f) 85 (m)
Eggs	*/week*	2	2	2-3	2-3 (f/m)	2-3 (f/m)
Fish	*g/week*	50	75	90	100 (f/m)	100 (f/m)

* 100 ml milk might be replaced by 15 g sliced cheese

If recommendations are fulfilled, sufficient intake of protein, fat, micronutrients, vitamins and energy is guaranteed
Amino acid mixture is no longer required

Protein controlled protocol

Age: 6 years
Body wheight: 20 kg
Body length: 119 cm

	Amount	Ingredients	Lys mg	Prot g	Fat g	Carb g	kcal
		Breakfast					
150	ml	Orange juice	13	1,0	0	13	65
		Cereal:					
40	g	Cereal	139	4,1	2	24	141
5	g	Coconut	15	0,4	3	0	33
100	g	Berry fruit	38	0,8	0	6	36
100	g	Fruit yogurt 3,5% fat	279	3,9	3	15	106
		Subtotal	484	10,3	9	58	381
		Snack					
50	g	Whole grain bread	116	4,2	1	21	116
10	g	Butter	5	0,1	8	0	74
15	g	Salami	248	2,9	5	0	56
40	g	Cucumber	11	0,2	0	1	6
		Subtotal	380	7,4	14	22	252
		Lunch					
160	g	Noodles (wheight boiled)	154	8,0	1	45	229
10	g	Olive oil	0	0,0	10	0	88
5	g	Onions	3	0,1	0	0	2
5	g	Tomato paste	5	0,1	0	0	2
50	g	Mushrooms	85	2,1	0	0	12
100	g	Tomatoe	36	1,0	0	3	20
40	ml	Vegetable stock	4	0,1	1	0	8
		Subtotal	287	11,3	12	49	361
		Snack					
100	g	Fruits	19	0,3	0	14	65
20	g	Chcocolate bar	72	1,3	4	13	96
		Subtotal	91	1,7	4	28	161
		Dinner					
50	g	Brown -wheat-bread	120	4,3	1	23	123
10	g	Butter	5	0,1	8	0	74
15	g	Sliced cheese, 45% fat	235	3,1	3	0	44
30	g	Pepper	18	0,3	0	1	7
150	ml	Cow milk 3,5% fat	425	5,1	5	7	98
		Subtotal	802	12,9	18	31	345
		Drinks					
700	ml	Water, tea	0	0,0	0	0	0
		Total per day	2045	43,5	57	188	1500
		Total per day/kg	102	2,2	2,9	9,4	75
		Energy in %		12	34	54	

Revision and translation of the parental guide

Work in progress…

Emergency treatment > 6 years

according to the current guideline

- *…the possibility that febrile illness or surgical procedures could cause subclinical cerebral damage in this age period cannot be excluded. Therefore,* ***emergency treatment after age 6 years should be liberally administered****.*

	Recommendation no. 9
Recommendation for research	Emergency treatment in children after age 6 years should be considered during severe illness or perioperative management and performed similarly to that in the age group 0–6 years, with individual adaptation.
Level of evidence	Low (SIGN level 3). Consistency of evidence is low.
Clinical relevance	Moderate.

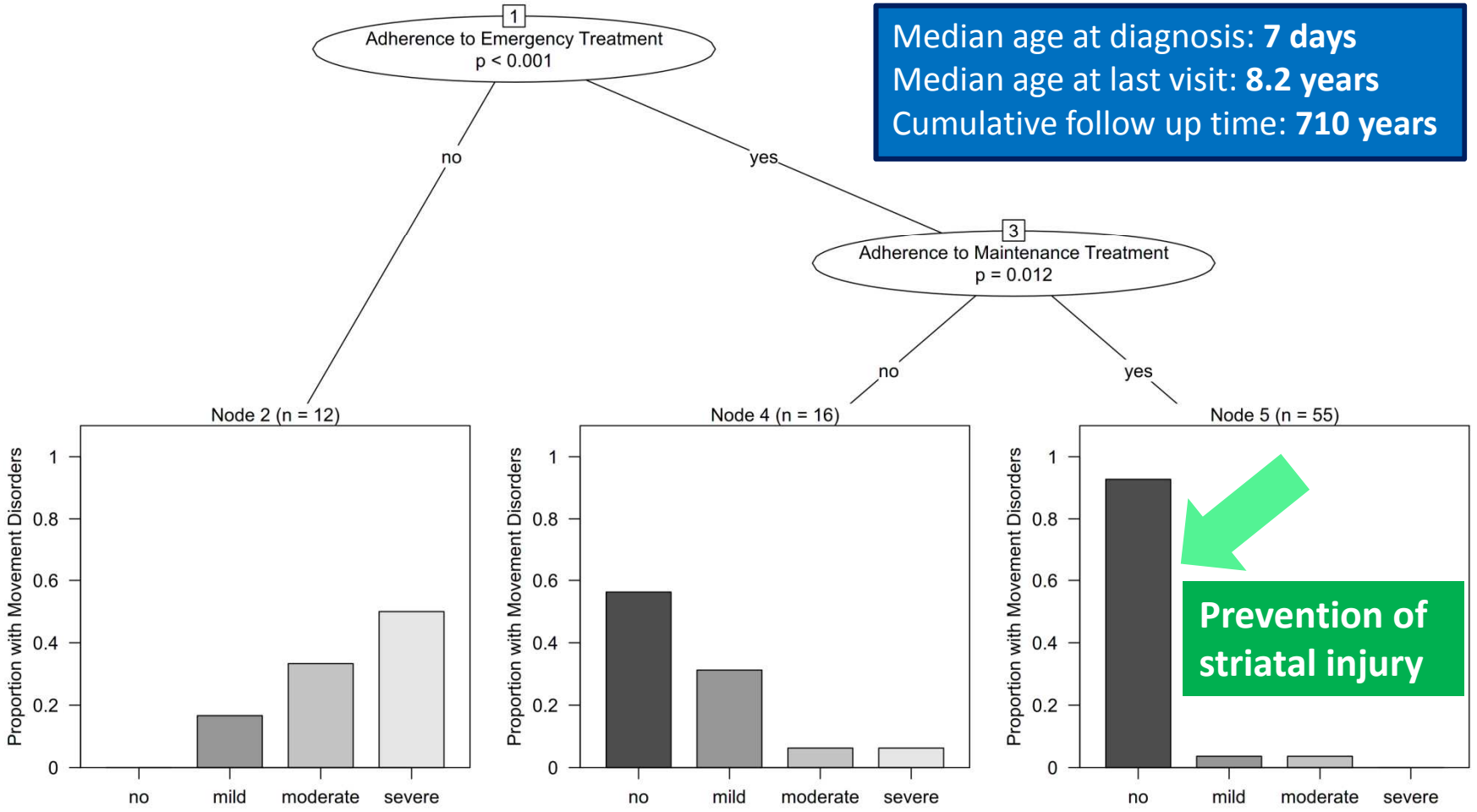
Boy et al. *J Inherit Metab Dis.* 2017; 40: 75-101.

EFFECT OF TREATMENT ON OUTCOME

Treatment adherence predicts neurologic outcome

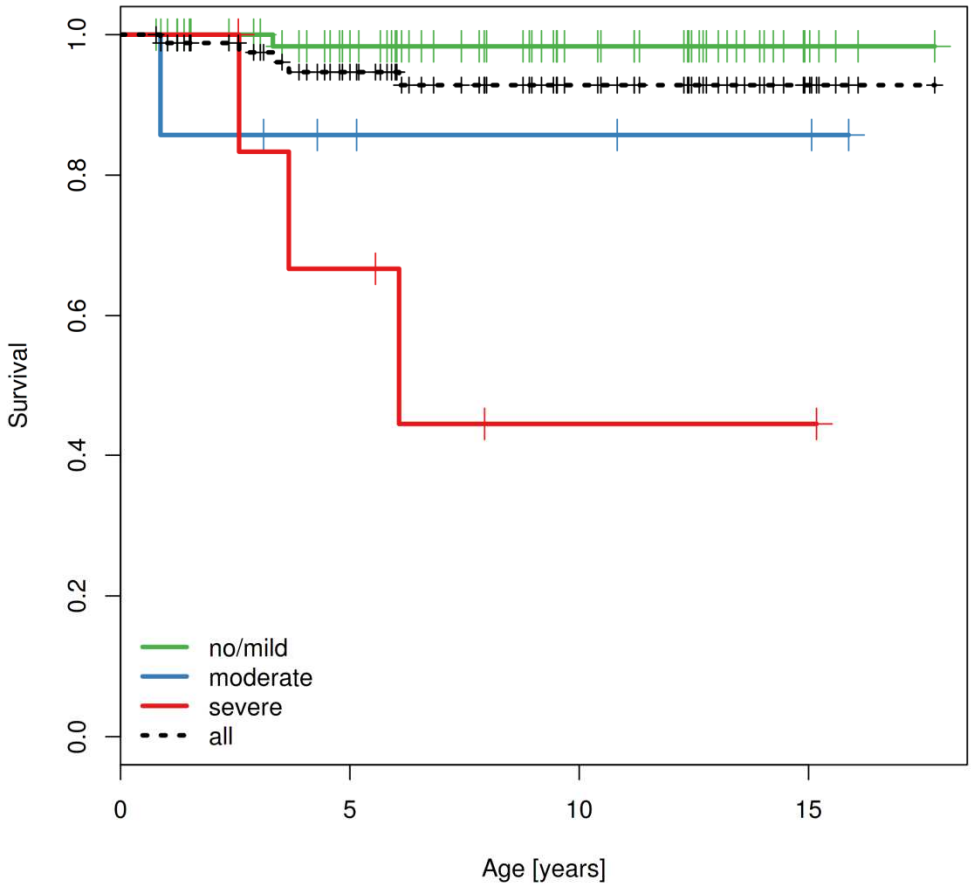
Prospective follow-up study on GA1 patients diagnosed by NBS in Germany, n=87

Median age at diagnosis: **7 days**
Median age at last visit: **8.2 years**
Cumulative follow up time: **710 years**



Emergency treatment	**No**	**Yes**	**Yes**
Low lysine diet	Yes or No	**No**	**Yes**

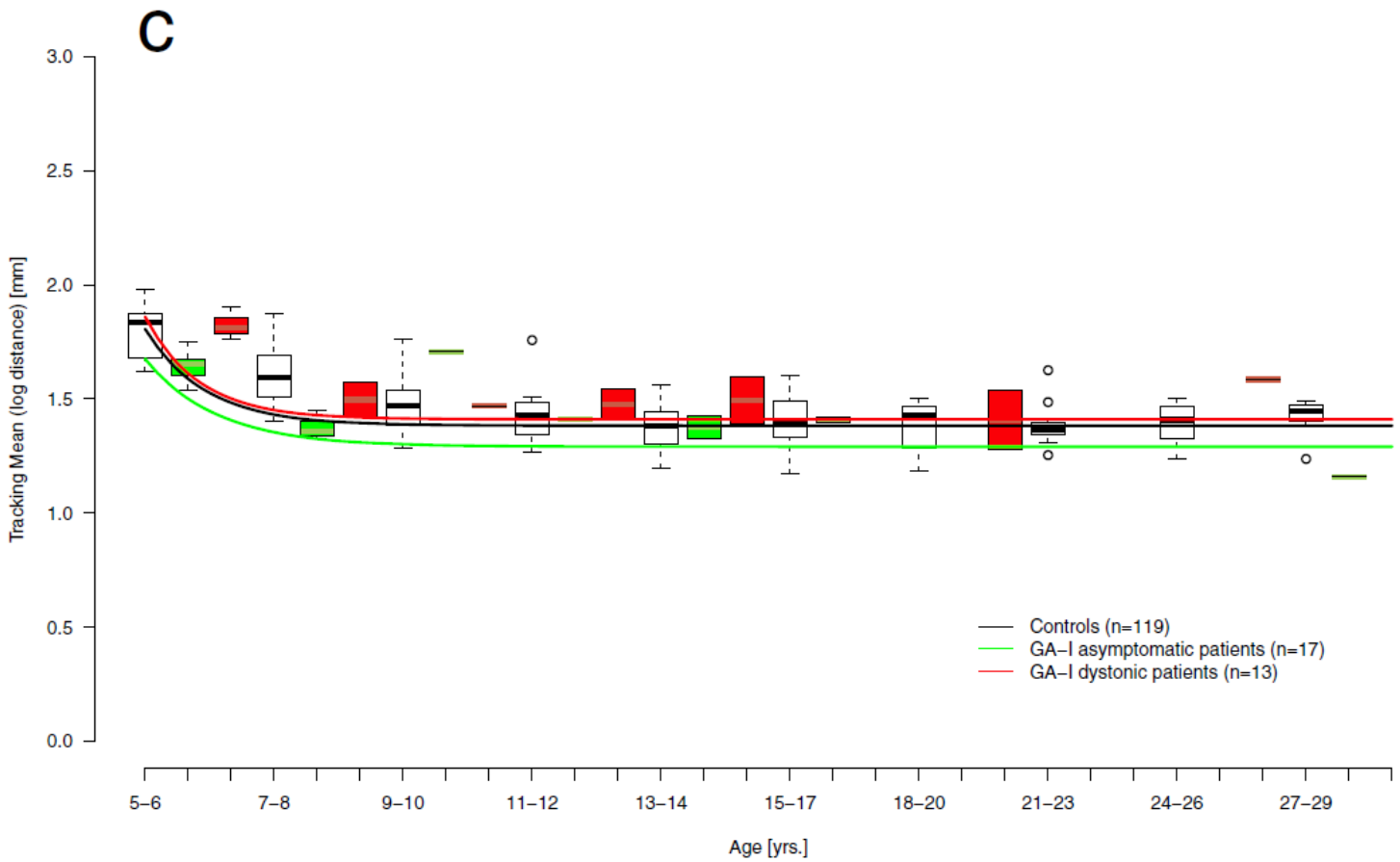
Severity of movement disorder predicts survival



Boy et al. *Ann Neurol* 2018*; 83: 970–979*

Normal development of neuropsychologic functions

No differences from controls in high cognitive load tests



Boy et al. *Orphanet J Rare Dis* 2015*; 10: 163*

Conclusions (1)

- Neurologic outcome in GA1 is strongly correlated with adherence to treatment recommendations

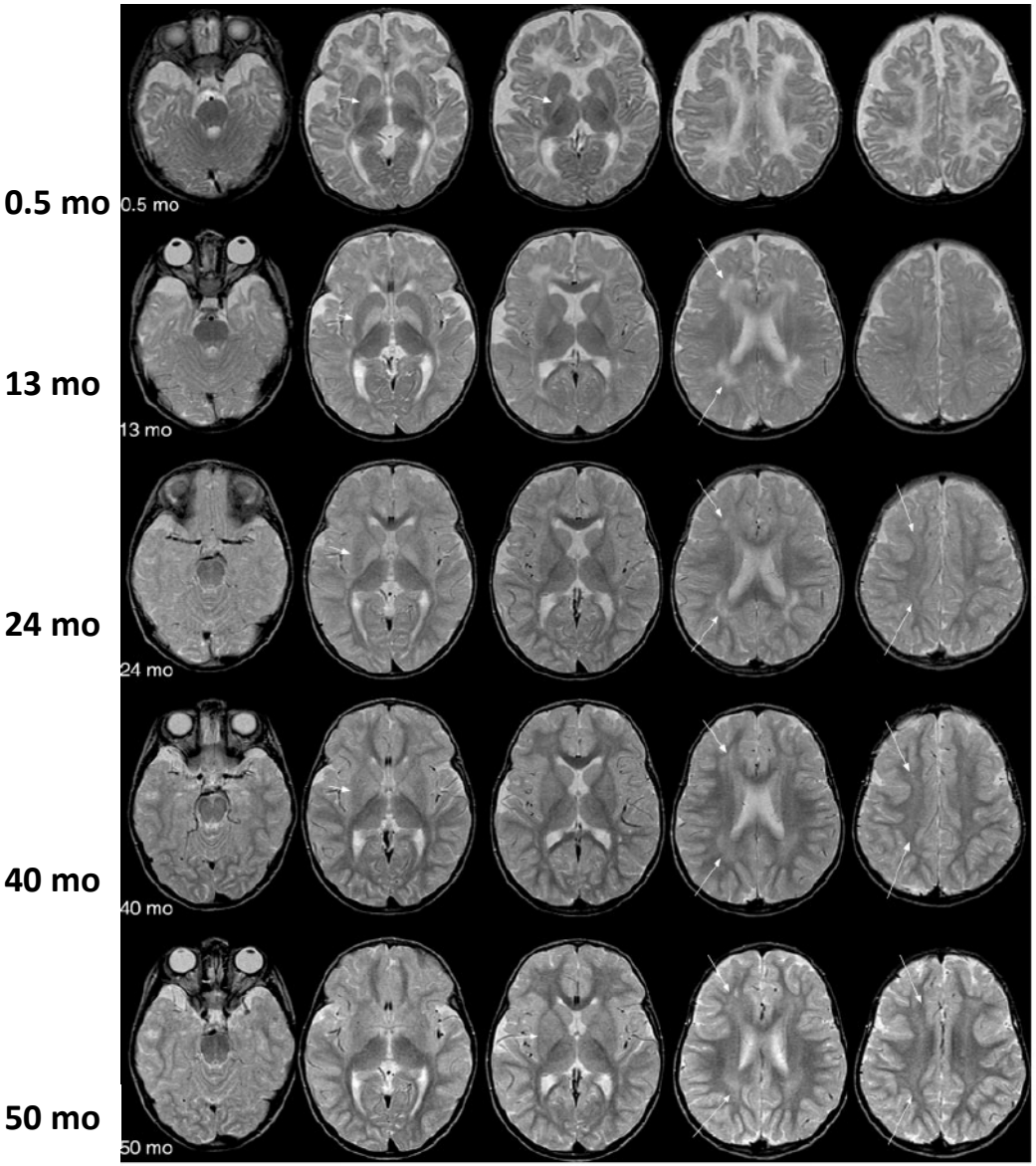
- In the majority of patients, guideline-according treatment starting in the neonatal period has a **strong positive effect** on:
- (1) **prevention of striatal injury**
- (2) **neurologic and neuropsychologic/cognitive functions**
- (3) **survival**

- Dietary treatment can be relaxed after age 6 years (‚*window of vulnerability*‘)
- The effect of dietary treatment *after* 6 years has not been systematically studied

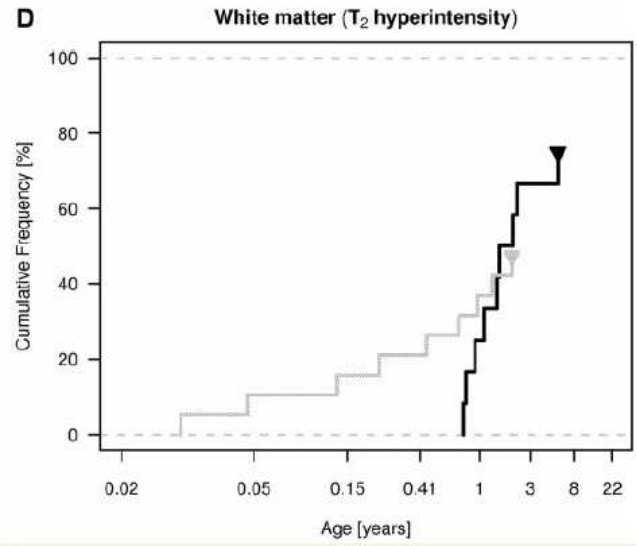
DISEASE PROGRESSION WITH UNKNOWN RELEVANCE: EXTRASTRIATAL AND RENAL MANIFESTATIONS

Extrastriatal abnormalities

highly dynamic, unknown clinical relevance



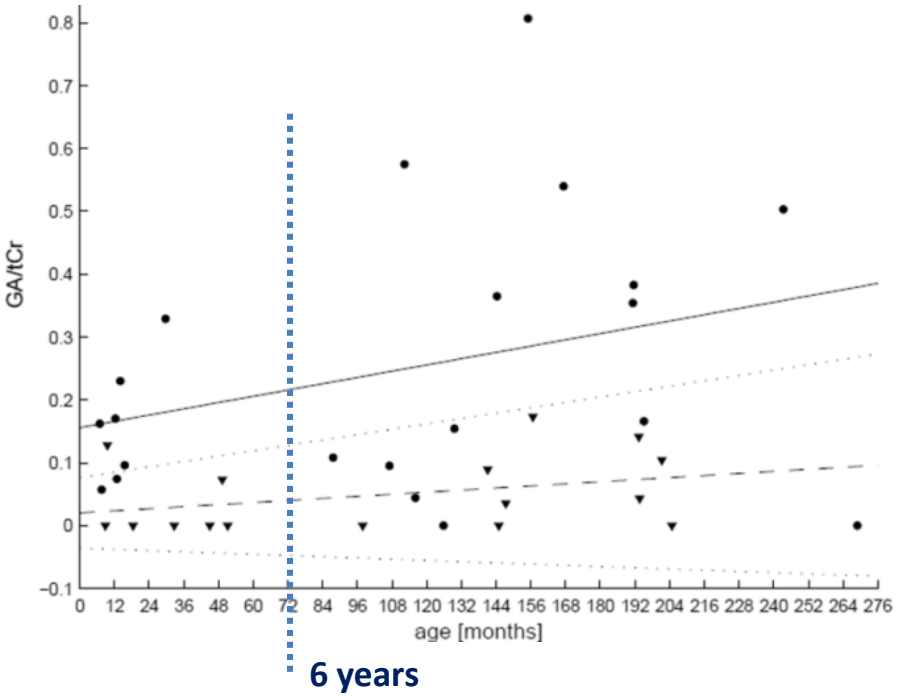
- Frontotemporal hypoplasia and pallidal hyperintensity may normalize
- White matter abnormalities **progress** & **frequency increases** with age

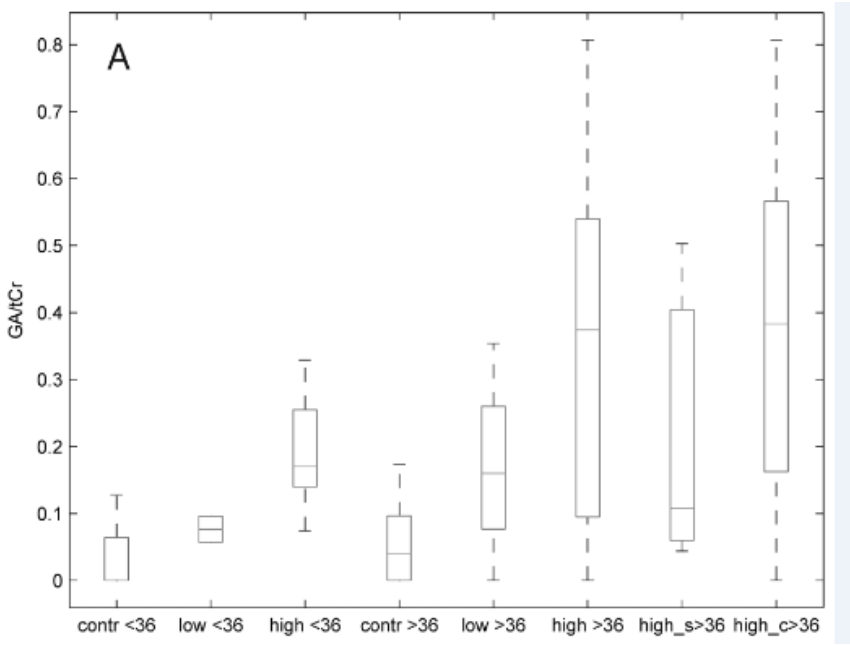


Harting et al. *Brain* 2009; 132: 1764-1782

HE phenotype as a risk factor for chronic neurotoxicity

^{1}H-MR spectroscopy study





→ High Excretors show **higher concentrations of neurotoxic metabolites** and **more white matter abnormalities** *with increasing age* compared to LE

→ Clinical relevance is unknown

Harting et al. *J Inherit Metab Dis* 2015; 38: 829-38

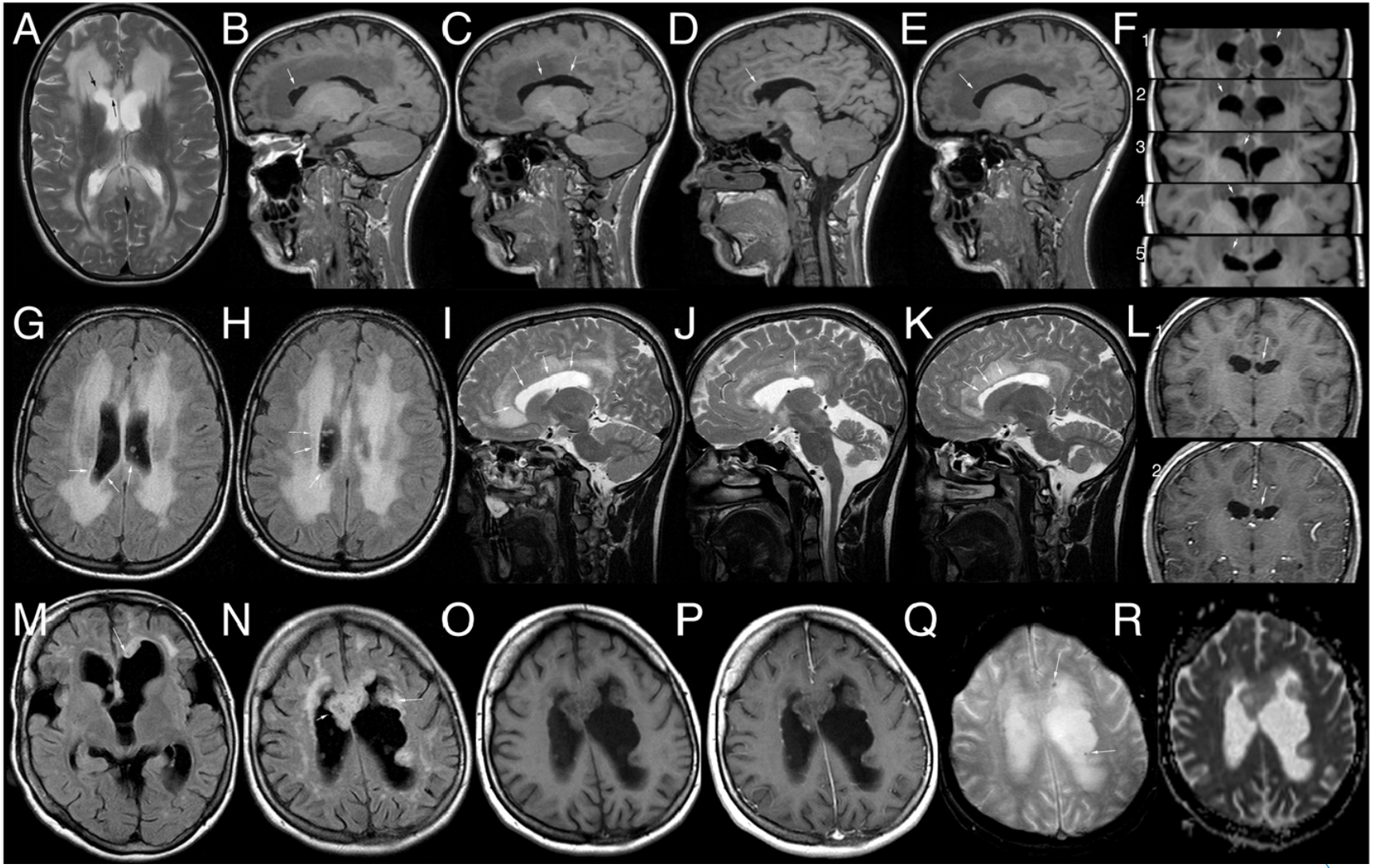
Extrastriatal abnormalities in patients diagnosed > 6 years („late onset“)

Subependymal nodules and white matter abnormalities: ***chronic neurotoxicity***

P1
15.7 yrs

P2
14.7 yrs

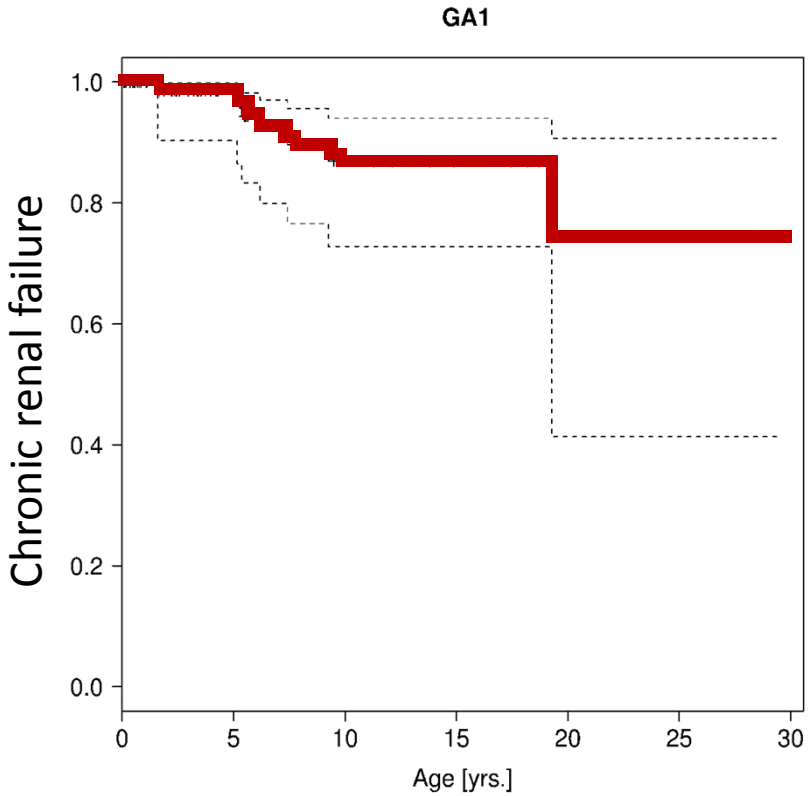
P6
25 yrs



Boy et al. *Orphan J Rare Dis* 2017; 12: 77

Evolving non-neurologic phenotype: Kidney function

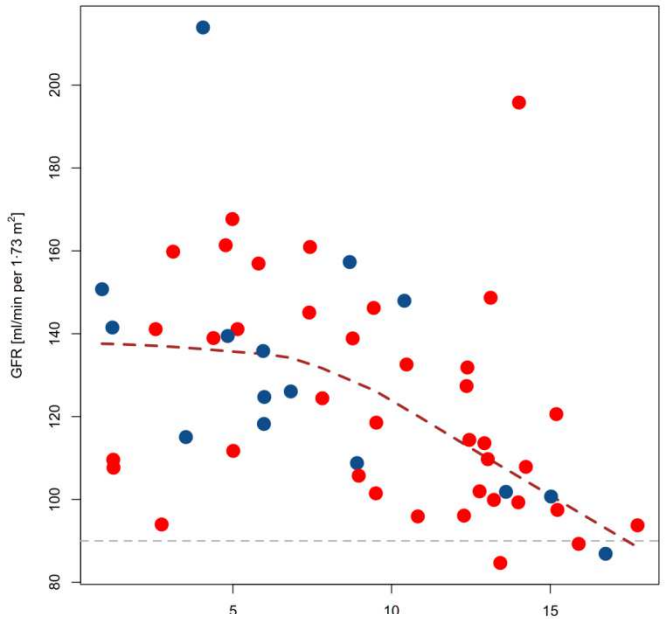
European registry and network for intoxication type metabolic diseases (E-IMD)



Kölker *et al. J Inherit Metab Dis* 2015; 38: 1059-1074

Kidney function (GFR) declines with age

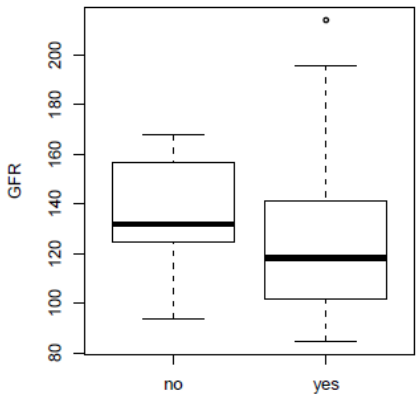
Prospective follow-up study on GA1 patients diagnosed by NBS in Germany, n=87



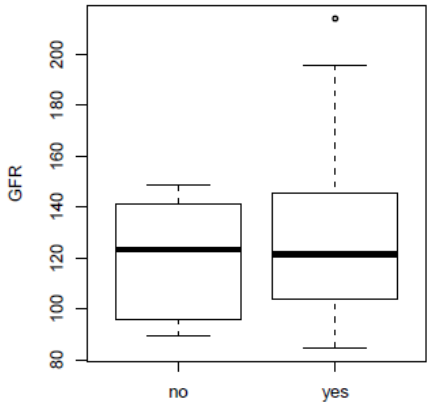
No difference between High (+) and Low Excretors (-)

Boy et al. *Ann Neurol* 2018*; 83: 970–979*

Maintenance treatment



Emergency treatment



No difference between treatment groups

Boy et al. unpublished

Conclusions (2)

After the '*window if vulnerability*', GA1 patients should continue (relaxed) dietary treatment > 6 years due to:

- uncertain longterm outcome
- risk of chronic neurotoxicity and progression of extrastriatal abnormalities (especially in high excretors/HE)
- risk of renal dysfunction (starting from childhood)

Although differing in extrastriatal and metabolite profiles, HE and LE patients share the same *clinical* course, and therefore should receive the same treatment

However, treatment does not seem to have an effect on

- (some) **extrastriatal abnormalities** (especially in HE patients)
- non-neurologic disease manifestations (**kidney function)**

but their clinical relevance is unknown

Thank you!

In vitro &
in vivo studies

Sven W. Sauer
Jürgen G. Okun
Roland Posset

Clinical studies,
Newborn screening,
Guideline
development

Stefan Kölker
Peter Burgard
Sven F. Garbade
Georg F. Hoffmann
Florian Gleich
Katharina Mengler
Jana Heringer
Inga Harting