Glut 1 Deficiency –
from infants to adolescents

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Glut 1 Deficiency –
from infants to adolescents

1. Introduction to Glut1D
2. from infants to adolescents
3. FAQs
Glucose is the essential fuel for the brain
Glut1D: diagnosis

- Lumbar puncture
  - CSF glucose ↓
  - CSF lactate ↓

- Mutations in the GLUT1 gene (SLC2A1)

- Glucose uptake assay
Glut1D: symptoms

- Epilepsy
  - Infantile seizures
  - Absence seizures
- Movement disorder
  - Spasticity
  - Ataxia
  - Dystonia
  - Chorea
- Cognitive/behavioral disturbances
  - Cognitive impairment
  - Delayed adaptive behavior
  - Variable attention

Classic phenotype
- Developmental encephalopathy

Pearson TS. 2013
Glut1D: treatment

- Glucose
- BBB
- KD
- Fat
- β-Ox.
- Ketones
- Acetyl-CoA
- TCA cycle
- Energy
- Brain

Energy
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- 3 : 1 KD
- 2 : 1 KD
- MAD (LGIT)

Atypical:
- migraine
- writer’s cramp
- alt. Hemiplegia
- ......
Long-Term Clinical Course of Glut1 Deficiency Syndrome

Aliza S. Alter, MD\textsuperscript{1}, Kristin Engelstad, MS\textsuperscript{1}, Veronica J. Hinton, PhD\textsuperscript{1,2}, Jacqueline Montes, PT, EdD\textsuperscript{1}, Toni S. Pearson, MD\textsuperscript{1}, Cigdem I. Akman, MD\textsuperscript{1}, and Darryl C. De Vivo, MD\textsuperscript{1}
Seizure types are variable:

- zyanotic spells = "turning blue"
- absence = "dreaming"
- focal = "one part of body"
- generalized = "entire body"
- myoclonic-astatic = "jerks & falls"
INFANTS

Paroxysmal eye–head movements in Glut1 deficiency syndrome

= “aberrant gaze saccades” are an early symptom of Glut1D
INFANTS & toddlers
Movement disorder
10%

„Absence“ Epilepsy
SCHOOL-AGE Epilepsy
SCHOOL-AGE

Movement disorder
Cognitive function:

**Strengths**
- Understanding language
- "Sequential" processing
- Pleasant kids, good social skills
- No decline

**Weakness**
- Active language
- Visual attention
- Motor skills
- "Whole picture" processing
ADOLESCENCE

PAROXYSMAL EVENTS

Questionnaire: n = 73

Klepper J et al, MovDisClinPract 2017
from infants to adolescents

- 3:1 KD
- 2:1 KD
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„What about the other Gluts?“
Glut1D: diagnosis in RBC

Gras D et al, Ann Neurol, epub

METAglut1

For the early detection of GLUT1 deficiency syndrome in a simple blood sample
Glut1D: diagnosis in RBC

Control

100%

Glut1D

quantitative Defect

50%

Glut1D

functional Defect

50%
„No mutation, no Glut1D?“

SLC2A1-negative patients:

Prof. Hans Scheffer
Institute of Human Genetics
Nijmegen, Netherlands
SLC2A1-positive patients

- heterozygous mutations
  - 85%
SLC2A1-negative patients
SLC2A1-negative patients?
What about other tissues?

Muscle?
Retina?
Placenta?
Heart?
ketogenic diets

Ketogenic Diet 4:1
- Ketosis: Ø, Taste: Ø

Ketogenic Diet 3:1
- Ketosis: ✓, Taste: Ø

Modified Atkins-Diet
- Ketosis: Ø, Taste: ✓

Low glycemic Index-Diet
- Ketosis: Ø, Taste: Ø

Regular diet
- Ketosis: Ø, Taste: Ø
Kass HR et al, Seizure 2016;35:83-87

Use of dietary therapies amongst patients with GLUT1 deficiency syndrome. \( n=92 \)

- **Efficacy:**
  - \( >50\% \) seizure control: 95%!
  - \( >90\% \) seizure control: 80%!

- duration 5.5 years
- 64% without AEDs
Outcome of ketogenic diets in GLUT1 deficiency syndrome in Japan: A nationwide survey.  n=39

- **Efficacy:**

  >90% seizure control: 80%!
The developing brain needs more energy!

Brain Energy demand

1y  6y  12y  adult

Ketogenic diets

KD - how long?
„What about atherosclerosis?

Grossbeck DK et al.
Long-term use of the ketogenic diet in the treatment of epilepsy.
Dev Med Child Neurol. 2006

\[
\begin{array}{lcccc}
\text{n = 28} & \text{Cholesterin ges.} & 201 \text{ mg/dl} & (>200) \\
& \text{Cholesterin HDL} & 54 \text{ mg/dl} & (<35) \\
& \text{Cholesterin LDL} & 129 \text{ mg/dl} & (>150) \\
& \text{Triglyceride} & 97 \text{ mg/dl} & (>200)
\end{array}
\]
10 patients, 10 years – long term follow-up of cardiovascular risk factors in Glut1D

Total cholesterol SDS

Triglycerides SDS
10 patients, 10 years – long term follow-up of cardiovascular risk factors in Glut1D

A. carotis Doppler

IMT, p = 0.63
Ketonesters (Triheptanoin)?

- C7-ketoester („artificial ketone“)
- used as tracer for butter in the EU
- liquid at RT with indifferent taste

![Diagram showing the metabolism of triheptanoin and fatty acids through the TCA cycle and ATP production.](image)
Triheptanoin-Study UX007

Design: - randomised, double-blind, placebo-controlled
- patients on KD excluded!

Randomisation

6 wks baseline

8 wks Study

“open-label extension period” => all patients on C7

Optional: C7 ff.

52 Wks

2 Studies: Triheptanoin for

1. EPILEPSY

2. Paroxysmal movement disorders
Increasing scientific interest

- "ketogenic diet" (Increasing from 800 in 2009 to 2000 in 2016)
- "Glut1 Deficiency" (Increasing from 150 in 2009 to 320 in 2016)
Diagnosis: genetic testing >> lumbar puncture

Brain MRI: white matter abnormalities in 1 of 4 patients!

Treatment: AED ineffective
MAD effective in 1 of 3 patients

early diagnosis & start KD: => better outcome
Glut1D gene therapy

Glut1D mouse  +  Adenovirus-ass. vector  →  Glut1D mouse  →  Monkey
These doctors - always need some help...!!
Well - interesting...

We have a great idea....!
Thank you to the sponsors
Thank you all!

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Save the date:

European Glut1D symposium
2018 London
2020 Paris
2022 Aschaffenburg !