Indianapolis (11–13 July 2012)

„International experience

Glut1 Deficiency

Joerg Klepper
Germany
The two places I work...

Matthews Friends Clinic, Lingfield, Surrey, UK

Childrens‘ Clinic, Aschaffenburg, Bavaria, GER
PART I:
Glut1 Deficiency

PART II:
Things we don’t know
21 years Glut1 Deficiency

 Patients

 Medline

 n=2

 n=84

 n=>200
International Glut1 Deficiency
The diagnosis

Fasting EEG

Lumbar puncture

Glucose uptake assay
SLC2A1 gene (1p35-31.3)

- heterozygous
- de novo / AD / AR
- hot spots, but no characteristic mutation
Glut1D genetics: „Lea“

wildtype $n=42$

Lea $n=62$
Glut1: 3-D Model

Zuniga FA et al, JBC (2001) 276; 48:44970-44975

Extracellular space

Cytoplasmic space
Glut1D genetics: „Marlies“
Microdeletions involving SLC2A1

- hypoglycorrhachia
- microcephaly
- high forehead
- small palpebral fissures
- epicantal folds
- broad convex nose
- short collumella
- flat philtrum
- flat occiput
- dysplastic ears
- retrognathia

Vermeer S et al
Dev Med Child Neurol

48 genes
incl. GLUT1
The classical phenotype

- Encephalopathy
- Epilepsy
- Movement Disorder
Movement disorder in Glut1D

Intention dystonia: 86%
Chorea: 75%
Intention tremor: 70%
Dyspraxia: 20.4%
Myoclonus: 16%

De Vivo et al, Movement Disorder 2010
Encephalopathy
Epilepsy
Movement Disorder
Seizure types are variable:

- zyanotic spells
- absence
- focal / generalized
- myoclonic-astatic
Seizure control on the KD:

Seizure severity

before KD

on KD

n = 15

Klepper et al, Neuroped 2005
The extended phenotype

- Paroxysmal Encephalopathy
- PEDystonia
- Absence Myoclonic-astatic Epilepsy

Movement Disorder

Epilepsy

Encephalopathy

Paroxysmal Absence

PEDystonia

Myoclonic-astatic

Movement Disorder

Epilepsy

Encephalopathy
Paroxysmal Encephalopathy
PEDystonia
Absence Myoclonic-astatic Epilepsy
Movement Disorder
Encephalopathy
paroxysmal exertion-induced dystonia (PED)

Weber YG et al
JCI 2008, May 1

GLUT1

exertion-induced energy deficit

Episodic basal ganglia dysfunction
Cation-leak via the GLUT1-defect
Stomatin-deficient cryohydrocytosis results from mutations in *SLC2A1*: a novel form of GLUT1 deficiency syndrome

Def.: AD inherited hemolytic anemias

=> RBCs „leaky“ to monovalent cations
=> mutations in transporter genes *RHAG* and *SLC4A1*

Stomatin is involved in:

- membrane organisation
- cholesterol-dependent regulatory processes
- possibly regulation of ion channels
- removal of misfolded or obsolete proteins
Paroxysmal movement disorders in GLUT1 deficiency syndrome
Zorzi et al. Neurology 2008;71;146-148
Glut1D: paroxysmal events

Questionnaire: n = 73

EVENTS:

Klepper J et al, unpublished data

“yes” 54
“no” 19
Glut1D: paroxysmal events

Duration

Klepper J et al, unpublished data
Glut1D: paroxysmal events

Klepper J et al, unpublished data
Glut1D: paroxysmal events

Klepper J et al, unpublished data
Absence epilepsy in Glut1D


10%
Absence epilepsies with widely variable onset are a key feature of familial GLUT1 deficiency

Mullen et al, Neurology 2010
Myoclonic-astatic epilepsy (Doose Syndrome)

- epilepsy syndrome of early childhood
- generalized seizures
- often resistant to medication

Mullen SA et al
Arch Neurol 2011

5%

Photo: world press
The treatment
The disease mechanism

Glucose

BBB

brain

Acetyl-CoA

TCA cycle

Energy
How the diet works

- **Glucose**
  - BBB
  - CNS
  - Acetyl-CoA
  - TCA cycle
  - Energy

- **KD**
  - Free fatty acids
  - $\beta$-Ox.
  - Ketones
The effect

before KD

4 months on KD
The ketogenic diets:

Ketogenic Diet 4:1

Ketogenic Diet 3:1

Modified Atkins-Diet

Low glycemic Index-Diet

Regular diet

ketosis

palatability
adverse effects

... in regard to Glut1D

Kossoff et al.
Empiric use of potassium citrate reduces kidney-stone incidence with the ketogenic diet.
Pediatrics (July 2009) 124:e300-e304

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<tr>
<th></th>
<th>patients</th>
<th>renal stones</th>
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<tbody>
<tr>
<td>+ K-citrate</td>
<td>198</td>
<td>4 (2%)</td>
</tr>
<tr>
<td>- K-citrate</td>
<td>105</td>
<td>11 (10%)</td>
</tr>
</tbody>
</table>
adverse effects
... in regard to Glut1D

- renal stones
- growth
- elevated lipids

- yes, we see it
- controversial

Treatment: (?)
- sufficient supplements !
- calories ↑ ?
- ketosis ↓ ?
- growth hormone ?

=> probably ok
adverse effects
... in regard to GLUT1DS

- renal stones
- growth
- elevated lipids

probably NO...

- lipid composition?
- alternative diets?
- drugs (statins)?
adverse effects
... in regard to GLUT1DS

- renal stones
- growth
- elevated lipids

**Cholesterol**

- $n = 10$

**Triglycerides**

- $n = 10$
KD: how long?

I. Intractable childhood epilepsy:

- 😞 2m
- 😊 2y

Kossoff, Epilepsia 2008
Freeman, Epilepsia 2008

II. GLUT1DS:

Brain Energy demand

1y 6y 12y adult
PART II:
Glut1 Deficiency

What we don’t understand:
Glut1 in brain

Multistep transport across the Blood-brain barrier
how astrocytes feed hungry neurons

The astrocyte-neuron lactate shuttle hypothesis

Astrocyte

Neuron

Glucose
Lactate
Ketones

TRENDS in Endocrinology & Metabolism Vol.12 No.4 May/June 2001
Glut1 function

Glut1 has two conformations for glucose binding

Glut1 is a functional dimer

sugar uptake site

sugar export site
ATP-binding sites

GLUT1 – cytosolic AMP
sugar import

GLUT1 – cytosolic ATP
Conformational change („cage“)
sugar recycling

Cloherty EK, Biochem (2002), 41, 12639-51
Liu Q, Biochem (2001), 40, 7874-81
Glut‘s: tissue distribution

- Muscle?
- Retina?
- Placenta?
- Heart?
Glut1 in the retina

Glut1 immunolocalization (green) in mammalian retina.

JCS 2010 123 (21):3639-3644
Lumbar puncture:

Other causes of hypoglycorrhachia:

- CNS infection
  - prolonged seizures
  - status epilepticus
  - cerebral shunt systems

Glut1D without hypoglycorrhachia:

- CSF glucose conc.: 2.6 mmol/l
- CSF glucose ratio: 0.52
- Mutation: Arg223Pro
Glucose uptake assay:

**A**

- Patient (n=74)
- Mother (N=73)
- Father (n=71)

**B**

GLUT1

**SLC2A1-negative patients:**

- 3%
- 15%
“black box” GLUT1

assembly 1

assembly 2

assembly 3

assembly 4

assembly 5
SLC2A1-positive patients

- heterozygous mutations
  - 85%

- GLUT1 uptake
- GLUT1 WB
SLC2A1-negative patients

- heterozygous mutations: 15%

- GLUT1 uptake
- GLUT1 WB
„hot-spot“ Arg126Cys

**9 patients:**

Arginine-126-Cysteine

![Chemical structures](Image)

<table>
<thead>
<tr>
<th>Patient</th>
<th>CSF ratio</th>
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<tbody>
<tr>
<td>1-2</td>
<td>N.D.</td>
</tr>
<tr>
<td>3-4</td>
<td>0.4</td>
</tr>
<tr>
<td>5-6</td>
<td>0.5</td>
</tr>
<tr>
<td>7-8</td>
<td>0.3</td>
</tr>
<tr>
<td>9</td>
<td>N.D.</td>
</tr>
</tbody>
</table>

Seizure onset:

![Graph](Image)
Newborn Screening for Glut1D?
Novel ketogenic diets in GLUT1DS?

Classic ketogenic diet:

- 4:1
- 3:1

Is it really necessary?

Modified Atkins diet:

- 1:1

Seems a good option .....

Low-glycemic Index diet:

Do they provide enough energy for the developing brain?

No experience …
Novel drugs (I)

**Alpha-lipoic acid** 10 mg/kg/d p.o.

- antioxidant, reduces inflammation
- Co-Enzyme in energy metabolism
- improves cellular glucose uptake
  (stimulates Insulin-Signal-Cascade: insulin effectiveness ↑)

- Alzheimer’s Disease
- Parkinson Disease
- Multiple Sclerosis
- **Diabetic Neuropathy**

**Klip et al (1994):**
- \(\alpha\)-LS improves Glucose transport
- in cultured muscle cells (GLUT4)
- via mobilization from intracellular pools

**Glut1D:** no convincing clinical evidence
Novel drugs (II)

Acetazolamide (Diamox) 500 mg p.o.

- carbonic anhydrase inhibitor
- promotes ion transport across the BBB
- modifies intracellular pH

- glaucoma
- altitude sickness
- cystinuria (diuretic)
- absence and myoclonic seizures
- idiopathic intracranial hypertension
- periodic paralysis
- episodic ataxia type I + II

Glut1D: totally suppressed paroxysmal dyskinesia
n=1, 18 y/o girl, (Ser294Pro)

Anheim et al, J Neurol 2010
Novel drugs (III)

Triheptanoin:

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

➢ supportive nutrient with the ketogenic diet?

Glut1D: no experience (yet)
Novel drugs (III)

Triheptanoin:

- **Glucose**
  - CNS
  - **Acetyl-CoA**
  - **Ketones**
  - **Energy**
  - **β-Ox.**
  - **Free fatty acids**

**Triheptanoin**

- **3 x**

**Anaplerotic effect (?)**

**TCA cycle**
animal models (n=4)

Heilig CW et al PNAS (2003) 100;15613-18


Jensen PJ et al JBC (2006) 281 (19);13382-87
Future treatment strategies

alternative substrates

stop inhibition

translocation

activation

transcription

mRNA

brain

gene transfer
Glut1D: European projects

- Clinical classification of Glut1D: AB, Nijmegen, London, (USA?)

- International Glut1D databank: AB, Heidelberg
  E-MAB European registry and network for metabolic diseases affecting the brain

- Next generation sequencing: AB, Nijmegen
  homozygosity mapping (looking for associated genes)

- Stomatin in Glut1D: AB, Bristol, UK
  Institute for Transfusion Sciences
Thank you

INDIANAPOLIS
11 – 13 July 2012

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