GLUT1-deficiency as treatable cause of Myoclonic-Astatic Epilepsy*

* amongst MANY other things

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Disclosure

Name of Commercial Interest

Type of Financial Relationship

Nothing to disclose
Learning Objective

Recognize the importance and diagnose the expanding spectrum of GLUT1-deficiency
NINDS Epilepsy Research Benchmarks

Research Objectives

Benchmarks Area I: Prevent epilepsy and its progression

Benchmarks Area II: Develop new therapeutic strategies and optimize current approaches to cure epilepsy

Benchmarks Area III: Prevent, limit, and reverse the comorbidities associated with epilepsy and its treatment
Benchmarks Area I: Prevent epilepsy and its progression

A. Identify as yet unrecognized causes of epilepsy (e.g., genetic, autoimmune and infectious).
Benchmarks Area II: Develop new therapeutic strategies and optimize current approaches to cure epilepsy

C. Optimize existing therapies and develop new therapies and technologies for curing epilepsy.
• **GLUT1** glucose transporter type 1
• **SLC2A1** solute carrier family 2 (facilitated glucose transporter), member 1

• Main route across blood-brain barrier
  • Erythrocytes
  • Glia

Gene knock-out  ➔ inadequate CNS glucose
GLUT1 Encephalopathy

De Vivo syndrome

• Onset in the first year of life
  • Low CSF glucose
  • Epilepsy
  • Intellectual disability
  • Microcephaly (variable)
  • Ataxia, spasticity & dystonia

• Ketogenic diet
  • Controls seizures
  • Less effective for intellectual development

Familial GLUT1 deficiency

Suls 2008, Brain vol131, p1831
Familial GLUT1 deficiency

Suls 2008, Brain vol131, p1831

• Paroxysmal exertional dyskinesia (PED)
  – Exertion induced
  – Exercised limbs

• Seizures
  – Generalised seizure types
  – Absence prominent

With or without mild Intellectual Disability
Ataxia
Complex Motor disorders
PED
Movement Disorder
Epilepsy and Movement Disorder
Epilepsy
Focal epilepsy
Refractory GGE
GGE
MAE
Intractable infantile epilepsy
Glut1 Encephalopathy
Increasing severity of phenotype
Mullen 2010, Neurology vol75 p432
Myoclonic-Astatic Epilepsy

Doose syndrome

- Previously well child
- Late infancy to early childhood (6mo – 6yrs)
- EEG looks like GGE
- Multiple seizure types

- Drop attacks (astatic seizures)
  - Myoclonic-atonic
- Potential epileptic encephalopathy
Myoclonic-Astatic Epilepsy

Doose syndrome

• Generalized spike-wave >2.5Hz
• Onset 7 months to 6 years
• Multiple seizure type
  • No tonics, no paroxysmal fast activity
• Drop attacks
  • Myoclonic-atonic
  • Atonic
  • Myoclonic

Mullen 2011, Arch Neurol vol 68 p1152
Myoclonic-Astatic Epilepsy

Doose syndrome

5%

4/84
<table>
<thead>
<tr>
<th>Gender/Age*</th>
<th>Sz onset</th>
<th>AEDs /Sz outcome</th>
<th>KD/age of initiation</th>
<th>Cognition</th>
<th>Neurological examination</th>
<th>Movement disorder</th>
</tr>
</thead>
<tbody>
<tr>
<td>M/15y</td>
<td>&lt; 36m</td>
<td>VPA+ESM; sz-free at 10yrs</td>
<td>Yes 13.5yrs</td>
<td>Normal early dev.</td>
<td>Tremor</td>
<td>PED – 6yrs</td>
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<tr>
<td>M/4y</td>
<td>8m</td>
<td>VPA sz-free at 3yrs</td>
<td>Yes 2.5yrs</td>
<td>Mild delay</td>
<td>Ataxia</td>
<td>_</td>
</tr>
<tr>
<td>M/12y</td>
<td>2yrs</td>
<td>VPA+TPM; sz-free at 8yrs</td>
<td>No</td>
<td>Normal early dev.</td>
<td>Ataxia</td>
<td>PED – 6yrs</td>
</tr>
<tr>
<td>M/28y</td>
<td>4yrs</td>
<td>VPA+LTG; sz-free at 24yrs</td>
<td>No</td>
<td>Mild ID</td>
<td>Normal</td>
<td>_</td>
</tr>
</tbody>
</table>
Early Onset Absence Epilepsy

Suls 2009, Ann Neurol vol66 p415

- Typical absence
  - Main seizure type
  - EEG
    - Generalised spike-wave
    - Absence recorded

- Onset under 4yo
- Excluded
  - Atypical absence
  - Tonic seizures
  - Atonic seizures
Early Onset Absence Epilepsy

1 in 10 have GLUT1-deficiency

4/34

(now 11/89)
Early Onset Absence Epilepsy

Arsov 2012, Epilepsia in press

• Epilepsy
  • Pure absence in most (8/11)
    • 2 with single GTCS, 1 with occasional Myoclonus
  • Mainly refractory (7/11)
  • Responds well to KD when used

• Other features
  • Normal intellect frequent (6/11)
  • PED rare (2/11)
  • Subtle (3/11) or severe ataxia (1/11)
  • Low-normal CSF glucose (2.3-2.4mmol/L)
    • Can be less than 2.2mmol/L
Early Onset Absence Epilepsy

- Electroclinical features not reliably different from the larger group of EOAE
  - Refractory to mild
  - Encephalopathic to normal development
Diagnosing GLUT1-deficiency

Classical De Vivo syndrome

• Infantile encephalopathy
• Seizures before 12 months (mainly after 2 weeks)
  • Electroclinically highly variable
• Motor disorders, developmental delay, microcephaly
• Lumbar puncture
  • Fasting CSF glucose <2.6mmol/L (90% <2.2mmol/L)
  • Normal lactate
Diagnosing GLUT1-deficiency

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LP in unexplained infantile epileptic encephalopathy
Diagnosing GLUT1-deficiency

Myoclonic-Astatic Epilepsy

- Difficult electroclinical pick
- PED specific but uncommon
- Onset may be in 2\textsuperscript{nd} to 5\textsuperscript{th} year of life
- Encephalopathy may be delayed or mild
- Lumbar puncture
  - 2/4 had LP, both had glucose <2.0mmol/L
- Sequencing or red cell uptake assay
Diagnosing GLUT1-deficiency

Early-Onset Absence Epilepsy

- Electroclinical differentiation difficult
- Lumbar puncture
  - Most low-normal (2.3-2.4mmol/L)
  - High pre-test probability (>10%)
- Sequencing
  - Consider even if LP equivocal
De Vivo syndrome

- Medication not particularly useful
  - <10% seizure free

- Ketogenic diet
  - High fat, very low carbohydrate
  - Production of ketone bodies
    - Transport via monocarboxylase transporters
    - Bypass GLUT1
  - Good but not perfect
    - ≈70% seizure free

Pong 2012; Epilepsia vol53, p1503
Treating GLUT1-deficiency

MAE and EOAE

• Broad range of severity
  • Mild EOAE
    • Seem to respond to AEDS
  • MAE
    • May respond but late and encephalopathy continues
• KD
  • Appears at least as effective for seizures
    • Limited numbers
Treating GLUT1-deficiency

Ketogenic Diet?

• GLUT1 encephalopathy
  • All the time (or near enough)
• MAE or EOAE
  • Refractory epilepsy
    • Seriously consider
• Evidence unclear for
  • Developmental improvement
  • Treatment of dyskinesia
• Less intensive diets (Atkins, Low GI)
Classical GGE

Arsov 2012, Ann Neurol in press

• Genetic (idiopathic) generalised epilepsy
  • Normal intellect
  • GSW
  • CAE (4yrs+), JAE, JME, GTCSA

• 504 cases, 470 blood bank controls
  • Sanger sequenced
  • Variants functionally assessed in *Xenopus oocytes*
Classical GGE

Rare coding variants

9/504 Probands with IGE

&

1/470 Controls
Classical GGE

Mutations affecting function

7/504 Probands with IGE (1.4%)
&

0/470 Controls
GGE  PED  * SLC2A1 mutation

wt Wild type
Classical GGE

• Dominant GLUT1 deficiency
  • 3/504 (0.6%)

• Other mutations
  • 4/504 (0.8%)
  • Can be associated with PED
  • Clear effect on protein function
  • Not seen in controls
NINDS Epilepsy Research Benchmarks

Benchmarks Area I: Prevent epilepsy and its progression

A. Identify as yet unrecognized causes of epilepsy (e.g., genetic, autoimmune and infectious).
Conclusions

• *SLC2A1* mutations leading to GLUT1-deficiency
  • Wide spectrum of phenotypes
  • Account for
    • GLUT1-encephalopathy
    • 10% of Early-onset absence epilepsy
    • 5% of Myoclonic-astatic epilepsy
    • 0.5-1% of Classical GGE
Conclusions

• Lumbar puncture
  • CSF glucose may be low-normal

• Mutation detection
  • Sequencing
  • Deletion screening
NINDS Epilepsy Research Benchmarks

Benchmarks Area II: Develop new therapeutic strategies and optimize current approaches to cure epilepsy

C. Optimize existing therapies and develop new therapies and technologies for curing epilepsy.
Conclusions

• Ketogenic diet
• Specific therapy
• Effective
Impact on Clinical Care and Practice

*SLC2A1* mutations leading to GLUT1-deficiency

• Common in Early Onset Absence Epilepsy and Myoclonic Astatic Epilepsy

• Test with lumbar puncture progressing to mutation detection and/or red cell glucose uptake

• Important treatment and genetic counseling implications to diagnosis
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Conclusions