Nutrition Management
Approaches to Nonketotic Hyperglycinemia (NKH)

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Disclosures

No relevant financial disclosures.
Learning Objectives

• Understand the pathophysiology and clinical characteristics of both the severe and attenuated forms of NKH

• Provide clinically applicable, evidence-based nutrition management approaches to NKH

• Identify the potential benefits and risks associated with the different nutrition management approaches to NKH when applied to the individual NKH patient
What is Nonketotic Hyperglycinemia (NKH)?

• Inborn error of metabolism
• Autosomal recessive
• Incidence: 1:76,000 estimated
• Defect in the enzyme system that breaks down the amino acid glycine, resulting in an accumulation of glycine in the body’s tissues and fluids
• AKA: glycine encephalopathy (rarediseases.org)
Breaking Down NKH

Two Forms of NKH

**Classical form**: caused by genetic mutations in the GLDC or AMT genes that encode the components of the glycine cleavage enzyme system

**Variant form**: caused by deficient enzyme activity, no mutation in the GLDC or AMT genes

(rarediseases.org)
Table: Classical Forms of NKH: Severe vs. Attenuated

<table>
<thead>
<tr>
<th></th>
<th>Severe Form</th>
<th>Attenuated Form (Poor, Intermediate, Good)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Onset</strong></td>
<td>First week of life</td>
<td>Neonatal period or later in infancy</td>
</tr>
<tr>
<td><strong>Initial Presentation</strong></td>
<td>Apnea on vent support, coma, hypotonia, lethargy, seizures</td>
<td>Hypotonia, lethargy, seizures</td>
</tr>
<tr>
<td><strong>Seizures</strong></td>
<td>Intractable, worsen over time</td>
<td>Treatable or absent</td>
</tr>
<tr>
<td><strong>Development</strong></td>
<td>Little to no progress</td>
<td>Variable, ranging from mild to profound impairment</td>
</tr>
<tr>
<td><strong>Common Challenges</strong></td>
<td>Airway maintenance, feeding, spasticity</td>
<td>Behavioral problems, hyperactivity</td>
</tr>
</tbody>
</table>

(genereviews.org, rarediseases.org)
NKH Treatment Goals

1. Reduce plasma glycine levels

2. Block glycinergic receptors

3. Symptomatic care, often in conjunction with many subspecialties
   • Gastroenterology for feeding difficulties
   • Neurology for seizure management
   • Pulmonology for respiratory support

There are NO curative treatments for NKH, but... there are those that can improve outcomes!

(genereviews.org, rarediseases.org)
Standard Pharmacological Therapies for NKH

- **Sodium benzoate**
  - to reduce plasma glycine levels
  - ↓ seizures and ↑ alertness
  - Need to closely monitor glycine levels

- **NMDA receptor site antagonists**
  - to block glycinergic receptors
  - ↓ seizures and ↑ alertness

- **Anticonvulsants**
  - for seizure management
  - Severe NKH typically on multiple anticonvulsants

Use for attenuated NKH, effect on severe NKH doubtful

(genereviews.com, rarediseases.org)
Hi all!
I JUST found out I am seeing an NKH in clinic tomorrow! It’s been awhile since I’ve followed an NKH!

Curious if clinics are restricting protein to DRI? How about restricting glycine? I feel like I’ve heard something about using a ketogenic diet for NKH, but I could be crazy!

Thanks soOo much in advance for your replies!

Sincerely,
Super Star Metabolic Dietitian drowning in biochemical pathways and plasma amino acids
Medical Nutrition Therapy for NKH: Protein/Glycine Restricted Diet

Restricting dietary glycine can aid in controlling plasma glycine levels in some individuals with severe NKH; however...

• Contribution of dietary glycine is low vs. the excess produced by endogenous synthesis and catabolism of glycine

• Often a mild bump up in sodium benzoate dose can compensate for increased dietary intake of glycine (genereviews.org)

• Severe glycine-restricted diet therapy for NKH has been associated with protein-malnutrition (Rogers et al 2014)
Medical Nutrition Therapy for NKH: Protein/Glycine Restricted Diet – Y or N!?

• Metabolic Dietitian and Multidisciplinary Team should weigh the costs vs. benefits of placing the individual NKH patient on a protein/glycine-restricted diet

• Important considerations:
  • Does adding the complexity of a strict diet or complicated formula recipe to the treatment regimen of NKH benefit the patient?
  • Can the same goal be achieved with a slight medication dose increase?

TAKE HOME MESSAGE: the limited, potential benefits of dietary glycine restriction often do NOT outweigh the complexities and risk!

(genereviews.org)
Medical Nutrition Therapy for NKH: Ketogenic Diet (KD)

• KD is a high-fat, low carbohydrate and protein restricted diet that causes a metabolic condition comparable to fasting

• Well-known non-pharmacological treatment for childhood epilepsy (Scholl-Bürgi et al 2015)

• May be of benefit to treating seizures in individuals with NKH
  • The exact mechanism of KD against epileptic seizures is unknown (Kava et al 2018)

• KD always lowers amount of glycine substantially, dose of sodium benzoate should be reduced accordingly to avoid benzoate toxicity (genereviews.org)
## Medical Nutrition Therapy for NKH: Ketogenic Diet (KD) in NKH Literature Review

<table>
<thead>
<tr>
<th></th>
<th>Cusmai et al 2012, n=3</th>
<th>Kava et al 2018, n=1</th>
<th>Currens 2019, n=1</th>
</tr>
</thead>
<tbody>
<tr>
<td>NKH neonatal form</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>Age KD initiated</td>
<td>&lt;12 months</td>
<td>&lt;12 months</td>
<td>11 yo</td>
</tr>
<tr>
<td>KD Ratio/KD Tolerance</td>
<td>4:1/Good</td>
<td>3.5:1/Good on 2(^{nd}) attempt</td>
<td>3:1/Good</td>
</tr>
<tr>
<td>Plasma Glycine Levels</td>
<td>Decreased</td>
<td>Decreased</td>
<td>Decreased</td>
</tr>
<tr>
<td>Seizure frequency &amp; severity</td>
<td>Decreased</td>
<td>Decreased</td>
<td>Decreased</td>
</tr>
<tr>
<td>Alertness</td>
<td>Increased</td>
<td>Increased</td>
<td>Increased</td>
</tr>
<tr>
<td>Quality of Life</td>
<td>Improved</td>
<td>Improved</td>
<td>Improved</td>
</tr>
<tr>
<td>Severe Psychomotor Delay</td>
<td>Continued</td>
<td>Continued</td>
<td>Continued</td>
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</table>
Case Report: 5 yo M with Severe NKH
Unrestricted Diet

- **Pertinent Medications:** sodium benzoate, multiple antiepileptics
- **Medical Nutrition Therapy:**
  - Estimated Protein Needs: 1.2-1.5 g/kg
  - Standard Pediatric Formula via GTube providing: 1.4 g/kg protein

Protein/glycine restricted diet not biochemically/clinically indicated.
KD trial discussed as option if seizure control worsens.

<table>
<thead>
<tr>
<th>Date</th>
<th>Plasma Glycine (120-400 umol/L)</th>
<th>Clinical Findings</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>August 2020</td>
<td>409</td>
<td>Increased seizure activity (daily + cluster seizures)</td>
<td>Weight adjusted sodium benzoate dose</td>
</tr>
<tr>
<td>November 2020</td>
<td>381</td>
<td>Seizures improved (“days” without seizures)</td>
<td>No changes</td>
</tr>
<tr>
<td>January 2021</td>
<td>No plasma amino acids drawn</td>
<td>Seizures still stable (1-2/week)</td>
<td>Neurology adjusted seizure meds December 2020</td>
</tr>
</tbody>
</table>
Case Report: 4 yo M with Severe NKH
Ketogenic Diet

- **Pertinent Medications:** sodium benzoate, multiple antiepileptics, dextromethorphan

- **Medical Nutrition Therapy:** KD diet initiated at 19 mo, 3.75:1 ratio currently

**KD has not reduced seizure activity.**

**KD decreased plasma glycine significantly →**

Sodium benzoate dose decrease, which has improved quality of life -- less irritable!

<table>
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<tr>
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<th>Plasma Glycine (120-400 umol/L)</th>
<th>Clinical Findings</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>July 2018</td>
<td>167</td>
<td>2-3 seizures/day</td>
<td>KD initiated</td>
</tr>
<tr>
<td>October 2018</td>
<td>80</td>
<td>Average 2-3 seizures/day, up to 6/day</td>
<td>Decreased sodium benzoate dose</td>
</tr>
<tr>
<td>December 2018</td>
<td>287</td>
<td>Less irritable, 3-6 seizures/day</td>
<td>KD continues</td>
</tr>
<tr>
<td>January 2019</td>
<td>288</td>
<td>“No significant seizure change”</td>
<td>KD continues</td>
</tr>
</tbody>
</table>
Thank you!

• Tailor medical nutrition therapy to meet the goals, abilities, and needs of the individual NKH patient and their family
• Work closely with the multidisciplinary team to achieve patient goals

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References


