GM3 Synthase Deficiency – A Potentially Treatable Disease?

**DDC Clinic mission:** To enhance the quality of life for people with special needs caused by rare genetic disorders
An Amish family with four children suffering from a devastating condition tried to find the answer.

In 1998, five families traveled hundreds of miles to PA to see Dr. Holmes Morton.

Among the five families, two (8 children) were affected by GM3 synthase deficiency.
Ganglioside GM3 Synthase Deficiency

- The mapping study performed on the 8 children identified ganglioside GM3 synthase deficiency (*Nat Genetics* 2004)
- Over 60 patients from OH, IN, KY, MI, NY, PA and WI have been diagnosed
- It has been recently reported in African American and European as well
...“It may be too late for us, but if we can help others with this center, we’ll gladly do that” ...

From an Amish father with 4 special needs children
Gangliosides

- A group of glico-lipids identified nearly a century ago
- Name derived from ganglion cells of brain from which these molecules were initially isolated
Ganglioside Synthesis Pathway

A key enzyme for ganglioside synthesis
Ganglioside GM3 Synthase Deficiency

- A complete lack of ganglioside GM3 and its biosynthetic derivatives
- An autosomal recessive disease
- Clinical manifestations: severe infantile irritability, intractable seizures, profound psychomotor developmental delay, completely caregiver dependent
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GM3 Deficiency - Potential Treatment

- Affected newborns appear normal for weeks to months after birth!
- Providing an adequate amount of GM3 might be effective treatment?
  - Cronassial and Sygen – Fidia of Italy
  - Buttermilk
  - Pig brain formula - DDC
  - G500 – commercial, natural gangliosides from milk
Sialic acid concentrations in brain cortex (adjusted for age at death and sex) of breastfed compared with formula-fed infants who died of sudden infant death syndrome.

Experimental Design

• To administer G500 (mainly GM3 and GD3) orally
• Dosage: 1g G500 (containing 5 mg GM3, 6 mg GD3)/kg body weight
• Assess the patients clinically and biochemically
  • Physical exams (weight, length and head circumference)
  • Parents’ reports
  • Developmental assessments (Battelle and Vineland)
  • Auditory evaluations (ABR and OAE)
  • EEG and imaging studies
  • Laboratory monitoring
• Three groups
  • Group 1 (pilot group): < 3 year-old (n=10)
  • Group 2: > 3 year-old (n=10)
  • Group 3: control (n=10)
## Clinical Assessments and Study Timeline

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<th>Pre-treatment 0 (month)</th>
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<td>Plasma ganglioside profile</td>
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<td>Comprehensive metabolic profile and anti-ganglioside antibody</td>
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- **Note:** The table includes assessments performed at various timepoints post-treatment. The symbols (•) indicate the frequency of testing at each interval.
Ganglioside GM3 Synthase Deficiency – Growth and Development
Ganglioside GM3 Synthase Deficiency – Growth and Development

A. Birth Weight

B. Birth Length

C. Birth Head Circumference

- Weight-for-Age Percentile
- Length-for-Age Percentile
- Head Circumference-for-Age Percentile
Children with GM3 Synthase Deficiency – Breast-fed vs Formula-fed
Typical Growth Charts in Children with GM3 Deficiency
Growth Charts in a 3 Year-Old GM3 Deficiency Boy on G500
Growth Charts of a 18 Month-Old GM3 Deficiency Girl on G500
• More focused, tracks better than children not on GM3 formula

• Gaining weight well and growing better than brother with GM3

• Holds head well, smiles more, tries to track

• Focus more, interacts better, smiles more

• Fussy periods seem less, follows better with eyes, more focused, less flailing of arms, trying to pull self up

• Smiles and laughs when touched, likes to be held more

• Gaining weight, head support better, coos a lot, smiles a lot, feel that vision is improving

• More content, vision continues to improve, sleeps better

• Better head control, therapists have commented on increased strength, feel she’s happier, less fussy, tracks better

• One parent reported no improvement
Developmental Assessments for Children with Ganglioside GM3 Synthase Deficiency

- GM3 children are difficult to assess due to the nature of their condition, but the comprehensive assessment is necessary.

- Assessment protocol included:
  - Structured administration of assessment instrument
  - Observation
  - Interviews with parents or other sources familiar with child
Developmental Assessments for Children with Ganglioside GM3 Synthase Deficiency

Criteria in choosing assessment tool:

- Standardized
- Reliable
- Being able to follow up for the changes
## Comparison of Assessment Content Measures

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<thead>
<tr>
<th>Vineland Adaptive Behavior Scales-II</th>
<th>Battelle Developmental Inventory-2</th>
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<tbody>
<tr>
<td>Measurement of adaptive behaviors including the ability to cope with environmental changes, including</td>
<td>Measurement of developmental milestones allowing adaptations for specific disabilities, including</td>
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<tr>
<td>- Fundamental socialization skills</td>
<td>- Cognitive skills</td>
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<td>- Communication skills</td>
<td>- Adaptive skills</td>
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<td>- Basic motor skills</td>
<td>- Motor skills</td>
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<tr>
<td>- Daily living adeptness</td>
<td>- Communication skills</td>
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<td>- Personal-social development</td>
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</table>
Preliminary Findings from Standardized Tests

- Areas with significant improvements after on G500 formula -
  - Coping skills in the Vineland Socialization Skills
  - Personal skills in the Vineland Daily Living Skills
  - Self Care in the Battelle Adaptive Skills

- Areas remaining relatively unchanged –
  - Gross motor and fine motor skills
Comparison of Battelle Inventory-2 between Two GM3 Deficiency Patients

No bar represents age equivalent of 0 m/o
A new liquid chromatography/tandem mass spectrometry method for quantification of gangliosides in human plasma

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Abstract

Gangliosides are a family of glycosphingolipids characterized by mono- or polysialic acid-containing oligosaccharides linked through 1,3- and 1,4-β glycosidic bonds with subtle differences in structure that are abundantly present in the central nervous systems of many living organisms. Their cellular surface expression and physiological malfunction are believed to be pathologically implicated in considerable neurological disorders, including Alzheimer and Parkinson diseases. Recently, studies have tentatively elucidated that mental retardation or physical stagnation deteriorates as the physiological profile of gangliosides becomes progressively and distinctively abnormal during the development of these typical neurodegenerative syndromes. In this work, a reverse-phase liquid chromatography/tandem mass spectrometry (LC/MS/MS) assay using standard addition calibration for determination of GM2, GM3, GD2, and GD3 in human plasma has been developed and validated. The analytes and internal standard
New Method for Plasma Ganglioside Profile Assay

- Using the robust PAEA&DMTMM chemical derivatization coupled with UPLC/MS/MS
- Approximately 10 time more sensitive than the previous method that we just published
- GM3 is detectable before the dietary GM3 supplementation
- Further studies are in progress to measure the downstream gangliosides (GT1a, GQ1b for example), and GM3 and GD3 in both red and white blood cells
Summary

- GM3 synthase deficiency causes severe postnatal growth and developmental retardations
- Gangliosides from breast milk are not sufficient to change the course of the disease
- Dietary supplements with substantial amount of GM3 provide some early promising results
- Much more work is needed in further understanding the condition
- The clinical trial and biochemical studies are ongoing
Acknowledgement

- Case Western Reserve University
- Cleveland State University
- Clinic for Special Children
- Metzenbaum School
- Northwestern University Medical School
- University Hospitals of Cleveland
- University of London, United Kingdom
- Wake Forest University