CONGENITAL MYASTHENIC SYNDROMES
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Declarations:

Contract with Jacobus Laboratories to study the effects of 3,4 DAP and its acetylated derivatives at the mammal neuromuscular junction.
CONGENITAL MYASTHENIC SYNDROMES

• Heterogeneous group of genetic diseases characterized by impaired neuromuscular transmission.

• Prevalence of CMS is 0.5 per 100,000.

• Similar symptoms and electrophysiological findings as in MG.

• Knowledge of type of CMS is mandatory.

• Effective treatment for one form of CMS may be deleterious or even fatal for a different type of CMS.

• Onset of symptoms of CMS is usually at birth but can occur any time in life.
Problems with the Diagnosis and Treatment of CMS:

- Limited experience, even among neuromuscular specialists.
- Lack of a simple confirmatory test.
- Electrodiagnostic tests difficult in pediatric patients.
- Conventional muscle biopsy is unhelpful.
- Genetic tests are commercially available but are expensive and require clinical guidance.
- CMS mutations are “private”, therefore gene testing involves arduous sequencing studies of large number of genes.
CONGENITAL MYASTHENIC SYNDROMES

- Mutations in any gene encoding a fundamental protein of the neuromuscular junction (NMJ) can result in a CMS.

- The protein encoded by the defective gene should not have a replacing isoform.

- Natural selection may explain an apparent inverse relationship between the gravity and the frequency of a CMS type.
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CLASSIFICATION OF CONGENITAL MYASTHENIC SYNDROMES

Presynaptic

Synaptic. Basal Membrane

Postsynaptic
CLASSIFICATION OF CONGENITAL MYASTHENIC SYNDROMES

- **Presynaptic**

- **Synaptic. Basal Membrane**

- **Postsynaptic**
  - AChR kinetic abnormalities
    - (CHRNA1-B1-D-E)
    1. slow channel syndrome
    2. fast channel syndrome
  - AChR deficiency
  - Escobar syndrome (CHRNG)
CLASSIFICATION OF CONGENITAL MYASTHENIC SYNDROMES

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   1. slow channel syndrome
   2. fast channel syndrome
b. AChR deficiency
c. Escobar syndrome (CHRNG)
d. Rapsyn deficiency (RAPSN)
CONGENITAL MYASTHENIC SYNDROME DUE TO RAPSYN MUTATIONS (*RAPSN*)

- arthrogryposis (15-75%)
- onset at birth (70%)
- respiratory insufficiency (35%)
- episodes of respiratory failure (resembling *CHAT* mutations)
- ophthalmoparesis rarely present
## Comparison of Phenotypes of Two Most Frequent Forms of CMS: Receptor Deficiency Due to Mutations in the Acetylcholine Receptor Epsilon Subunit Gene and Rapsyn

<table>
<thead>
<tr>
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<th>Epsilon Subunit</th>
<th>Rapsyn</th>
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<tbody>
<tr>
<td><strong>Defective Gene</strong></td>
<td>CHRNE</td>
<td>RAPSN</td>
</tr>
<tr>
<td><strong>Prenatal Manifestations</strong></td>
<td>NO</td>
<td>Diminished fetal movements</td>
</tr>
<tr>
<td><strong>Arthrogryposis</strong></td>
<td>NO</td>
<td>May be present</td>
</tr>
<tr>
<td><strong>Facial Deformities</strong></td>
<td>NO</td>
<td>May be present</td>
</tr>
<tr>
<td><strong>Age of Onset</strong></td>
<td>Birth or infancy</td>
<td>Birth or any time in life</td>
</tr>
<tr>
<td><strong>Ophthalmoparesis</strong></td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td><strong>Respiratory Crisis</strong></td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Treatment</strong></td>
<td>AChE inhibitors</td>
<td>AChE inhibitors</td>
</tr>
<tr>
<td></td>
<td>3,4-DAP</td>
<td>3,4-DAP</td>
</tr>
</tbody>
</table>
CLINICAL CASES
Deficiency of Receptors due to $CHRNA1\ 459\text{insG/L296I}$

RNS at 2Hz before and after neostigmine
Deficiency of Receptors due to \textit{RAPS}N mutations
Before 10 mg 3,4 DAP
Deficiency of Receptors due to *RAPSN* mutations
After 10 mg 3,4 DAP
CLASSIFICATION OF CONGENITAL MYASTHENIC SYNDROMES

Presynaptic
a. Deficiency of ChAT (CHAT)

Synaptic. Basal Membrane

Postsynaptic
a. AChR kinetic abnormalities (CHRNA-B-D-E)
   1. slow channel syndrome
   2. fast channel syndrome
b. AChR deficiency
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d. Rapsyn deficiency (RAPSN)
CMS DUE TO IMPAIRED ACh RESYNTHESIS/CHAT; INFANTILE ONSET
CMS DUE TO IMPAIRED ACh RESYNTHESIS/CHAT; INFANTILE ONSET

14 year-old boy and a 16 year-old sister with lifelong history of weakness in the lower extremities precipitated by exercise. No history of episodic apneas

DNA Analysis

Exon 7: L210P and P211A

genetic analysis
CMS DUE TO \textit{CHAT} MUTATIONS; NEONATAL ONSET (\textit{CHAT} p.Arg207RHis)
CMS DUE TO *CHAT* MUTATIONS;  *CHAT R207H*
NEONATAL ONSET

**Phenotype**

**Endplate morphology**

**Ultrastructure of the NMJ**

**R207 localization in ChAT**
CLASSIFICATION OF CONGENITAL MYASTHENIC SYNDROMES

Presynaptic
  a. Deficiency of ChAT (*CHAT*)

Synaptic. Basal Membrane
  a. Deficiency of AChE (*COLQ*)

Postsynaptic
  a. AChR kinetic abnormalities
     (*CHRNA-B-D-E*)
     1. slow channel syndrome
     2. fast channel syndrome
  b. AChR deficiency
  c. Escobar syndrome (*CHRNG*)
  d. Rapsyn deficiency (*RPSYN*)
ENDPLATE ACETYLCHOLINESTERASE DEFICIENCY

- Frequent (12-15% of CMS), disabling and with early onset in life.
- Limited therapeutic options.

- ptosis
- sluggish pupillary response
- external ocular movements
- facial weakness
- limb weakness
- respiratory crisis
- repetitive CMAP
- frequency-dependent decrement
- mutations in COLQ

COLQ mutations
Ultrastructure of the NMJ
**ENDPLATE ACETYLCHOLINESTERASE DEFICIENCY**

Electrophysiology

- **normal EPP**
- **prolonged EPP in deficiency of AChE**

**Mechanism of repetitive action potentials**

**Staircase summation of EPPs during AChE inactivation**

**Treatment:**

- Acetylcholinesterase inhibitors (not effective)
- Sympathomimetic drugs (Ephedrine, Albuterol), usually effective.
- Fluoxetine (not effective)
- 3,4-Diaminopyridine (increases release of ACh by blocking presynaptic K⁺ channels), sometimes effective, but theoretically may increase endplate damage.

**Experimental:**

- Ito M, Suzuki Y, Okada T, Fukudome T, Yoshimura T, Masuda A, Takeda S, Krejci E, Ohno K. A single IV adeno-associated virus serotype 8 (AAV8)-COLQ to Colq(-/-) mice recovered motor functions, synaptic transmission and morphology of NMJ. ColQ-tailed AChE was restored to 89% of the wild type.
- Stem cells
SLOW CHANNEL SYNDROME (CHRNA1, CHRN1, CHRN2, CHRN3, CHRN4)

- **Dominant, progressive** and usually severe form of CMS.
- Predominant involvement of cervical and of wrist and finger extensor muscles.
- When severe, respiratory crises are frequent.
- Repetitive CMAP to single nerve stimulus.
- Decrement may be absent.
- Prolonged synaptic potentials and currents.
- Cationic overload of the endplate resulting in an “endplate myopathy”.
- Responsive to ion channel blockers such as quinidine or fluoxetine.
SLOW CHANNEL SYNDROME (*CHRNA1*, *CHRNB1*, *CHRND*, *CHRNE*)

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**Presynaptic**
- a. Deficiency of ChAT (*CHAT*)

**Synaptic. Basal Membrane**
- a. Deficiency of AChE (*COLQ*)
- b. Deficiency of agrin (*AGRN*)

**Postsynaptic**
- a. AChR kinetic abnormalities (*CHRNA-B-D-E*)
  1. slow channel syndrome
  2. fast channel syndrome
- b. AChR deficiency
- c. Escobar syndrome (*CHRNG*)
- d. Rapsyn deficiency (*RAPSN*)
- e. Deficiency of MuSK (*MUSK*)
- f. Deficiency of Dok-7 (*DOK7*)
- g. Deficiency of Lrp4 (*LRP4*)
CLASSIFICATION OF CONGENITAL MYASTHENIC SYNDROMES

Presynaptic
a. Deficiency of ChAT (CHAT)

Synaptic. Basal Membrane
a. Deficiency of AChE (COLQ)
b. Deficiency of agrin (AGRN)
c. Deficiency of Laminin β2 (LAMB2)

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a. AChR kinetic abnormalities (CHRNA-B-D-E)
   1. slow channel syndrome
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b. AChR deficiency
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f. Deficiency of Dok-7 (DOK7)
e. Deficiency of Lrp4 (LRP4)
Mutations in *LAMB2* causing a severe form of synaptic congenital myasthenic syndrome

R A Maselli, J J Ng, J A Anderson, O Cagney, J Arredondo, C Williams, H B Wessel, H Abdel-Hamid, R L Wollmann
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Presynaptic
a. Deficiency of ChAT (CHAT)

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a. Deficiency of AChE (COLQ)
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b. AChR deficiency
c. Escobar syndrome (CHRNG)
d. Rapsyn deficiency (RPSYN)
e. Deficiency of MuSK (MUSK)
f. Deficiency of Dok-7 (DOK7)
e. Deficiency of Lrp4 (LRP4)
h. Deficient of GFPT1 (GFPT1)
i. Deficient DPAGT1 (DPAGT1)
# Comparison of Phenotypes of Limb-Girdle Myasthenia Due to Mutations in DOK7 and GFPT1

<table>
<thead>
<tr>
<th>Defective Gene</th>
<th>DOK7</th>
<th>GFPT1</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age of Onset</strong></td>
<td>Birth to 1st or 2nd Decade of Life</td>
<td>1st or 2nd Decades of Life</td>
</tr>
<tr>
<td><strong>Ptosis</strong></td>
<td>Frequent</td>
<td>Rare</td>
</tr>
<tr>
<td><strong>Ophthalmoparesis</strong></td>
<td>Possible</td>
<td>Rare</td>
</tr>
<tr>
<td><strong>Bulbar</strong></td>
<td>Frequent</td>
<td>Rare</td>
</tr>
<tr>
<td><strong>Respiratory Involvement</strong></td>
<td>Frequent</td>
<td>Rare</td>
</tr>
<tr>
<td><strong>Tubular Aggregates in Muscle Biopsy</strong></td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Response to AChE Inhibitors</strong></td>
<td>Poor</td>
<td>Good</td>
</tr>
<tr>
<td><strong>Response to 3,4-DAP</strong></td>
<td>Poor</td>
<td>Good</td>
</tr>
<tr>
<td><strong>Response to Albuterol</strong></td>
<td>Good</td>
<td>Unknown</td>
</tr>
</tbody>
</table>
Limb-Girdle Myasthenia due to *DOK7* mutations.
Limb-Girdle Myasthenia due to *GFPT1* mutations.
DIAGNOSTIC FLOWCHART FOR WORKUP OF CONGENITAL MYASTHENIC SYNDROMES

Patient background:
- arthrogryposis?
- epidermolysis bullosa?
- congenital nephrosis?
- CNS symptoms?

• MUSCLE FATIGUE AND WEAKNESS
• EMG DECREMENT
• NEGATIVE ANTB.
• NL MUSCLE Bx.

Family background:
- consanguinity?
- Gypsies
- North Africans?
- Jewish from Iran/Iraq?

Dominant?

Recessive or negative family history?

early onset?

birth

infancy

late onset?

CHRNE/A1/B1/D
RAPSN
CHAT
COLQ (↓ AChE)

CHRNE/A1/B1/D
RAPSN
CHAT
COLQ (↓ AChE)
DOK7
MUSK

RAPSN
DOK7
GFPT1
DPAGT1
AGRN
MUSK
LAMB2

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CHRNE/A1/B1/D
RAPSN
CHAT
COLQ (↓ AChE)

CHRNE/A1/B1/D
RAPSN
CHAT
COLQ (↓ AChE)
DOK7
MUSK

RAPSN
DOK7
GFPT1
DPAGT1
AGRN
MUSK
LAMB2

Repetitive CMAP?

+ slow channel syndrome

CHRNE/A1/B1/D

- different disease? more than one gene? consanguinity?

specific gene sequencing exome sequencing

diagnostic procedures
Recessive or negative family history

- pattern of muscle weakness
  - ocular
    - CHRNE/A1/B1/D
    - COLQ (↓ AChE)
    - AGRN
    - LAMB2
    - CHAT
  - bulbar
    - CHRNE/A1/B1/D
    - RAPSN
    - CHAT
    - DOK7
    - AGRN
    - MUSK
  - limb-girdle
    - RAPSN
    - DOK7
    - GFPT1
    - DAPGT1
    - ALG2
    - ALG14

- special features
  - stridor (DOK7)
  - apnea (CHAT, RAPSN)
  - retinitis pigm.? (GFPT1)
  - Epidermolysis bull. (PLEC1)
  - arthrogryposis (RAPSN)
  - nephrosis (LAMB2)
  - ocular anomalies (LAMB2)
  - facial anomalies (RAPSN)
  - tubular aggregates (GFPT1)
  - core-like lesions (DOK7)

- mental developmental delay
- comparative genomic hybridization microarray

Gene Sequencing

- +
  - diagnosis and treatment
- -
  - exome sequencing
  - muscle biopsy
    - motor point
    - anconeus intercostal

Diagnostic procedures
Acknowledgments

• Patients and parents of patients
• NIH (5R01NS049117-03)
• Muscular Dystrophy Association
• The Myasthenia Gravis Foundation of California