Inherited Disorders of Neuromuscular Transmission – from gene discovery to tailored treatments

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Forward Look Session
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Hanns Lochmüller
Institute of Genetic Medicine, Newcastle University, Newcastle upon Tyne, UK
CMS: Diagnostic Criteria

Clinical Criteria:
- myasthenic syndrome: exercise induced muscle weakness
- early onset of disease: birth / first years of life (< 2 years)
- no response to immunosuppressive treatment
- treatment with anticholinesterase drugs may lead to improvement

Neonatal:
- poor suck and cry, choking spells, ventilatory failure, ptosis; symptoms worsened by crying or activity

Infancy, childhood:
- delayed motor milestones; seldom learn to run
- cannot climb steps well; abnormal fatigability on exertion
- cannot keep up with peers in sports
- Ptosis; fixed or fluctuating ocular palsies
- Spinal deformities, reduced muscle bulk
The neuromuscular junction - structure

Muscle fiber

Motor end-plate

Nerve

(Uehara and Desaki, in Salpeter, 1987; Ed.)
<table>
<thead>
<tr>
<th>Component</th>
<th>Gene</th>
<th>Chromosome</th>
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<tbody>
<tr>
<td>ChAT</td>
<td>CHAT</td>
<td>10q11</td>
</tr>
<tr>
<td>ColQ</td>
<td>COLQ</td>
<td>3p25</td>
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<tr>
<td>LAMB2</td>
<td>LAMB2</td>
<td>3p21</td>
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<td>AGRN</td>
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<td>ChAT deficiency</td>
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<td>endplate-AChE deficiency</td>
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<td>Kinetic changes of AChR/</td>
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<td>endplate-AChR deficiency</td>
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<td>AChR)</td>
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<tr>
<td>muscle-specific kinase</td>
<td>MUSK</td>
<td>9q31</td>
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<tr>
<td>downstream of kinase 7</td>
<td>DOK7</td>
<td>4p16</td>
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<tr>
<td>Sodium channel, voltage-gated</td>
<td>SCN4A</td>
<td>17q23</td>
</tr>
<tr>
<td>glutamine:fructose-6-phosphate</td>
<td>GFPT1</td>
<td>2p13</td>
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<td>amidotransferase</td>
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Identified genetic defects in a large CMS cohort (Munich, 1997-2011)

Most frequent!

- MUSK
- DOK7
- CHRNA1
- CHRND
- CHAT
- CHRNB1
- GFPT1
- RAPSN
- COLQ
- CHRNE

no mutation
**CHRNE mutations leading to AChR deficiency: clinical clues**

- **Onset of disease:** early infancy, typically within the first year of life
- **Clinical symptoms:** ptosis, fixed ophthalmoparesis, weakness of bulbar muscles, in general mild phenotype and benign course of disease
- **Very rare:** respiratory insufficiency, severe generalized weakness
- **Anticholinesterase medication:** clearly positive response to short-term and long-term treatment
LG-CMS represent a significant proportion of total CMS cases
Onset usually in the first years of life, but late-onset is possible.

First symptom: limb girdle weakness (waddling; sometimes inward rotation of knee and feet).

Other frequent symptoms: ptosis, respiratory crisis (often with need for assisted ventilation).

Mestinon ineffective for the long-term (sometimes worsening).
LG-CMS with tubular aggregates – a distinct entity

- Limb girdle weakness
- No ophthalmoplegia, no ptosis
- Benefit from esterase inhibitors
- No mutations in DOK7
- Mutations in GFAT or DPAGT
Zebrafish as animal model
Reduced number and size of AChR clusters after downregulation of Dok-7

Neuromuscular junctions at 48 hpf
Slow-twitch muscle fibre morphology is altered after downregulation of Dok-7

Slow-twitch muscle fibres and acetylcholine receptors at 48 hpf
DOK-7 knockdown in Zebrafish - summary

- Dok-7 deficient zebrafish have less and smaller neuromuscular junctions and motility defects
- Dok-7 deficiency leads to misalignment of slow muscle fibres. This is a previously unrecognised function of Dok-7 outside the NMJ
- This function is MuSK independent, as MuSK deficiency causes a more severe loss of acetylcholine receptors, but leaves slow muscle fibres intact
- Zebrafish are a good animal model for studying the neuromuscular junction
<table>
<thead>
<tr>
<th>Defect</th>
<th>Gene</th>
<th>Therapy</th>
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<tbody>
<tr>
<td>Cholin-Acetyltransferase Deficiency</td>
<td>CHAT</td>
<td>AChEI, prophylactic use for apnea prevention!</td>
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<tr>
<td>Endplate AChE Deficiency</td>
<td>COLQ</td>
<td>ephedrine? AVOID AChEI!</td>
</tr>
<tr>
<td>Receptor Deficiency</td>
<td>CHRNA-E</td>
<td>AChEI, 3,4 Diaminopyridine</td>
</tr>
<tr>
<td>Slow Channel Syndrome</td>
<td>CHRNA-E</td>
<td>Fluoxetine, AVOID AChEI!</td>
</tr>
<tr>
<td>Fast Channel Syndrome</td>
<td>CHRNA-E</td>
<td>AChEI, 3,4 Diaminopyridine</td>
</tr>
<tr>
<td>Rapsyn Defect</td>
<td>RAPSN</td>
<td>AChEI, prophylactic use?</td>
</tr>
<tr>
<td>Sodium channel, voltage-gated</td>
<td>SCN4A</td>
<td>AChEI?? (1 family)</td>
</tr>
<tr>
<td>MuSK (muscle-specific kinase)</td>
<td>MUSK</td>
<td>AChEI ?? (1 family)</td>
</tr>
<tr>
<td>Dok-7 (downstream of kinase 7)</td>
<td>DOK7</td>
<td>ephedrine, albuterol/salbutamol?</td>
</tr>
<tr>
<td>GFPT1/GFAT1</td>
<td>GFPT1</td>
<td>AChEI</td>
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Summary

- CMS are clinically very variable, genotype-phenotype correlations are difficult to establish. However, there are some clues pointing towards the underlying genetic defect.

- Detection of the genetic defect is important for the selection of the appropriate drug therapy.

- Clinical vigilance for neuromuscular transmission defects is key to accurately diagnose and treat patients with CMS.

- Standard clinical trials may be difficult, but standardized follow-up of patients and international collaboration may help to improve standards of care and therapy.
Joint Research for DMD

Website & Communications

TACT

Standards of Diagnosis & Care

Outcome Measures

Care & Trial Site Registry

Patient Registries

BioBank

Three year work plan

2007-2011
EU funded Network

2012 onwards
Alliance funded through multiple streams with global partners & membership

Governance
Chair – Hanns Lochmüller
Vice – Annemieke Aartsma-Rus

Executive Committee
Supported by academic advisory board ("task force") of NMD leaders

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Thank you to all sponsors, referring clinicians, patients and families!