What’s New in OPMD?

OPMD Patient and Family Conference
April 13, 2013
Oculopharyngeal Muscular Dystrophy (OPMD):

1915: Taylor et al. describe clinical phenotype

1962: Victor et al. identify disease as a muscular dystrophy

1998: Brais et al. identify gene mutation

2012: Treatment still palliative

From Myology: AG Engel
Epidemiology of OPMD

- Worldwide prevalence 1:100,000
- Geographic clusters with high prevalence
  - French Canadians
  - Bukhara Jews in Israel
  - Hispanic New Mexicans
- Likely the most common muscular dystrophy in New Mexico
  - Estimated prevalence 10:100,000 or higher
  - Unique opportunity to study this disease

Becher et al., JAMA. 2001;286(19):2437-2440
“Nucleotides” that make up DNA:

- Adenine
- Thymine
- Guanine
- Cytosine
PABPN1 Mutation in OPMD (Poly-A Binding Protein Nuclear 1)

Expansion from \((GCG)_6\) to \((GCG)_{8-13}\) in exon 1 of PABPN1 gene
Role of PABPN1

• PABPN1 occurs in all cells of body, catalyzes “polyadenylation” of nearly all mRNAs and controls length of polyadenine tail
• Yet mutation clinically affects certain skeletal muscles late in life . . .
Normal muscle tissue under microscope

Rimmed vacuoles
OPMD

• Unique “clumps” of filaments in the muscle nuclei – “intranuclear inclusions”

• **SPECIFIC** for OPMD
Electron micrograph of a muscle fiber showing a nucleus with a clear area occupied by intranuclear inclusions. Bar, 0.1 um.

Therapeutic Development Pipeline

- Drug Discovery: 10,000 Compounds, 6.5 years
- Pre-clinical: 250 Compounds, 6 years
- Clinical Trials: 5 Compounds, 1.5 years
- FDA Review
- Clinic

1 approved drug
Lingering question: Is size of the GCN expansion related to severity of disease?

- GCN 8
- GCN 9 (Hispanic New Mexicans)
- GCN 10
- GCN 11
- GCN 12
- GCN 13

Increasing expansion size
Genotype and phenotype study of 34 Spanish patients diagnosed with oculopharyngeal muscular dystrophy

- No correlation was observed amongst the size of the mutation, the age of onset, and severity of symptoms.
- This fact suggests that other conditions apart from the OPMD gene mutation could influence the age of onset and the severity of the symptoms.

OPMD and the brain

• OPMD does not usually affect the brain

• However, cognitive decline has been described in homozygous GCN₁₃ patients – those with 2 copies of the mutation, not just one copy (Blumen et al, 2009, Neurology)
Extensive neuropsychological and neuropsychiatric evaluations were performed on 11 OPMD heterozygote patients (one copy of the mutation)

OPMD patients were less efficient than a matched control sample on several tests, particularly those using executive functions

There was a negative correlation between GCN expansion size and some neuropsychological scores – could brain involvement be linked to larger expansion size?

Naples, Italy
OPMD and the brain: New Mexico

• We have **not** seen homozygous patients in the UNM clinic

• Only 5% of patients we have seen in clinic had memory problems documented in their medical history
In order to conduct clinical trials (test new therapies in OPMD), we need a way to measure how the disease is progressing.

Can imaging of muscles help?

MRI machine
Quantitative MRI can detect subclinical disease progression in muscular dystrophy

- Examined 8 patients with genetically confirmed OPMD and 5 healthy volunteers twice at an interval of 13 months.
- Performed muscle MRI of the thighs
- **Quantitative MRI measurements did change in OPMD patients over the 13 month study period**
- Quantitative MRI might, therefore, be a useful tool for monitoring disease progression in future therapeutic trials.

Progressive myopathy in an inducible mouse model of oculopharyngeal muscular dystrophy

- New “mouse model” of OPMD
- When the mice expressed mutant PABPN1, they developed skeletal and cardiac muscle problems.
- Nuclear inclusions of PABPN1 were seen under the microscope (as in OPMD patients)
- When researches decreased the mutant PABPN1 levels in the mice, the muscle became healthier
- These results support association between mutant PABPN1 accumulation and muscle damage in mice. Resolution of muscle damage in mice suggests that the disease process in OPMD patients may be treatable

New treatments can be tested first in animals or in cells in petri dish
Antiprion drugs 6-AP and GA reduce PABPN1 toxicity and aggregation in oculopharyngeal muscular dystrophy

• Drosophila model of OPMD
• The drugs 6AP and GA alleviate OPMD in Drosophila flies, including muscle degeneration and nuclear inclusion formation
• 6AP and GA may be general anti-aggregation molecules

Barbezier N et al, EMBO Mol Med 2011. Montpellier, France
Is apoptosis ("programmed cell death") a factor in OPMD?
Over-expression of BCL2 rescues muscle weakness in a mouse model of oculopharyngeal muscular dystrophy

• Blocking apoptosis improves muscle disease in some mouse models of other muscular dystrophies
• This study showed that apoptosis is not only involved in the pathology of OPMD but also is a major contributor to the muscle weakness and dysfunction in this disease
• Genetically blocking apoptosis by over-expressing BCL2 temporarily improves muscle weakness in a mouse model of OPMD (A17 mice)

• Thus, while apoptosis is a major pathway that causes muscle weakness in OPMD, other cell death pathways may also contribute to the disease when apoptosis is inhibited.

Davies JE and Rubinsztein DC, Hum Mol Genet. 2011 Cambridge, UK
Atrophy, fibrosis, and increased PAX7-positive cells in pharyngeal muscles of oculopharyngeal muscular dystrophy patients

Gidaro T et al., J Neuropathol Exp Neurol 2013. Paris, France
Cricopharyngeal Muscle

- The cricopharyngeal muscle (CPM) is the main muscle of the upper esophageal sphincter (UES).
- The precise mechanism by which PABPN1 expansion primarily affects this specific muscle in OPMD is still unknown.
- Studied muscle biopsies from 14 OPMD patients, 3 inclusion body myositis patients, and 9 healthy controls

Gidaro T et al., J Neuropathol Exp Neurol 2013. Paris, France
In OPMD patients’ cricopharyngeal muscles (n = 6), there were typical dystrophic features with extensive endomysial fibrosis (scarring) and marked atrophy (thinning) of muscle fibers.

No fibrosis detected in control muscles or unaffected opmd muscles.

No signs of regeneration seen in the cricopharyngeal muscles of OPMD patients.
Cricopharyngeus muscle may have difficulty regenerating and is prone to scarring

• Intranuclear inclusions were present in all OPMD muscles but unaffected OPMD patient muscles (i.e. sternocleidomastoid, quadriceps, or deltoid; n = 14) did not show evidence of fibrosis or atrophy.

• These results suggest that the specific involvement of CPM in OPMD might be caused by failure of the regenerative response and exacerbated fibrosis (scarring) that does not correlate with the presence of PABPN1 inclusions.

Gidaro T et al., J Neuropathol Exp Neurol 2013. Paris, France
Therapeutic Development Pipeline

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FDA Review

Clinic
Summary

• Nearly 20 major studies of OPMD have been done in the last 3 years, all around the world
• Research has been both clinical (involving patients) and laboratory (involving animals and cells)
• Advances made in understanding why muscle cells are sick in OPMD
• A few agents have shown benefit in animals/cells
• Eventually, we need to test therapies in patients through **CLINICAL TRIALS**!
  – Let’s figure out what we need to do to make this happen...
Questions
Patient Registries: Why We Need Them

OPMD Patient and Family Conference

April 13, 2013
Our government wants to figure out how to treat rare diseases

25 million Americans have a rare disease!
Patient Registries

- Databases where patient information, including medical information and family history, is collected and stored in a standardized and secure way.

- Combined data is used for medical research, epidemiologic or other research studies.

- Registries can be used to recruit patients for clinical trials to learn about a particular disease or condition; to develop therapeutics, or for improving and monitoring the quality of health care.
Next up: OPMD Registry
Future Directions

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Clinical Characteristics and Health Outcomes of Oculopharyngeal Muscular Dystrophy in a Single-Center Longitudinal Cohort
Pathway to Therapies for OPMD

2004-2012: Transgenic mouse models of OPMD (Hino, Dion, Davies, Trollet, Mankodi)

2006: Drosophila model of OPMD (Chartier)

2005: Doxycycline attenuates disease in transgenic mouse model (Davies)

2006: Trehalose delays pathology in transgenic mouse model (Davies)

Need:
- Better natural history data
- Outcome measures to assess treatment response

Clinical trials
Aims and Methods

• To describe the clinical characteristics, comorbidities, and health outcomes of a cohort of patients with OPMD seen at our center

• Retrospective chart review of patients seen between January 1, 2000 and December 31, 2011
88 cases analyzed thus far

- 95% New Mexico
- 2% Colorado
- 2% Texas

60% female
40% male

Histogram: Age at first neurology visit for 88 OPMD patients

Mean age at first neurology clinic visit: 64 ± 9 yr

Among the 60% of patients with two or more visits to neurology, the median duration of follow-up was 3.2 yrs (IQR=4.8 yrs)
Genetic and family data

• 57% had genetic testing showing a GCN expansion in the PABPN1 gene
  – all were heterozygous for the GCN₉ allele
• 98% of individuals had two or more relatives in two or more generations affected with the disease
• 220 total children of affected individuals (as documented by history in the medical record)
Basic clinical data

• 99% had ptosis
• 100% had dysphagia
• Mean age of onset of ptosis:
  – 53 ± 7 yrs (range 39-70 yrs)
• Mean age of onset of dysphagia:
  – 54 ± 8 yrs (range 39-77 yrs)
• 32% of individuals reported experiencing weight loss in the period preceding the first clinic visit
  – Among these individuals, the median patient-reported weight loss was 9 kg (IQR=13 kg)
<table>
<thead>
<tr>
<th>Interventions</th>
<th>Percentage of individuals (n=88)</th>
<th>Median # of procedures per person*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgical correction of ptosis</td>
<td>77%</td>
<td>1</td>
</tr>
<tr>
<td>Esophageal dilatation</td>
<td>30%</td>
<td>1</td>
</tr>
<tr>
<td>Botulinum toxin injection to cricopharyngeus muscle</td>
<td>14%</td>
<td>3</td>
</tr>
<tr>
<td>Cricopharyngeal myotomy</td>
<td>2%</td>
<td>1</td>
</tr>
<tr>
<td>Feeding tube</td>
<td>8%</td>
<td>N/A</td>
</tr>
</tbody>
</table>

* Among those who had the procedure

Mean BMI was significantly lower among patients who had PEG tube versus those who didn’t (17 vs 26, p=.0003)

Comparing those who had a dysphagia procedure (dilatation, botox, or myotomy) versus those who did not, there was no significant difference in the mean BMI of the two groups (24 versus 26, p=0.11)
Creatine kinase

- 25% of individuals (n=22) had creatine kinase measurements at some point during follow-up
- Among these individuals, the median CK was 147 IU/L (range 47-881 IU/L)
<table>
<thead>
<tr>
<th>Motor function</th>
<th>Percentage of individuals</th>
</tr>
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<tbody>
<tr>
<td>Difficulty walking (patient report)</td>
<td>30%</td>
</tr>
<tr>
<td>Difficulty climbing stairs (patient report)</td>
<td>41%</td>
</tr>
<tr>
<td>Difficulty arising from floor, squat or chair (patient report or examination)</td>
<td>56%</td>
</tr>
<tr>
<td>Proximal lower extremity weakness on examination</td>
<td>83%</td>
</tr>
<tr>
<td>Proximal upper extremity weakness on examination</td>
<td>66%</td>
</tr>
</tbody>
</table>
28% of subjects progressed in need for adaptive equipment during the neurology follow-up period.

<table>
<thead>
<tr>
<th>Adaptive equipment</th>
<th>Percentage of individuals</th>
<th>Mean age</th>
<th>Mean CK</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>74%</td>
<td>65±9 yrs (n=65)</td>
<td>246 (n=16)</td>
</tr>
<tr>
<td>Hand-held adaptive equipment (cane, walker, crutch)</td>
<td>22%</td>
<td>68±10 yrs (n=19)</td>
<td>130 (n=5)</td>
</tr>
<tr>
<td>Wheelchair or scooter</td>
<td>4%</td>
<td>77±6 yrs (n=4)</td>
<td>92 (n=1)</td>
</tr>
</tbody>
</table>

Mean ages are different
<table>
<thead>
<tr>
<th>Co-morbidity</th>
<th>Percentage</th>
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<tbody>
<tr>
<td>Acid reflux</td>
<td>43%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>39%</td>
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<tr>
<td>Arthritis</td>
<td>33%</td>
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<tr>
<td>Cataract</td>
<td>28%</td>
</tr>
<tr>
<td>Depression/anxiety</td>
<td>28%</td>
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<tr>
<td>Diabetes</td>
<td>24%</td>
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<tr>
<td>Hearing impairment</td>
<td>23%</td>
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<tr>
<td>Pneumonia</td>
<td>18%</td>
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<tr>
<td>Asthma/COPD</td>
<td>17%</td>
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<tr>
<td>Heart condition</td>
<td>16%</td>
</tr>
<tr>
<td>Cancer</td>
<td>15%</td>
</tr>
<tr>
<td>Cognitive impairment</td>
<td>5%</td>
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<tr>
<td>Kidney</td>
<td>2%</td>
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<tr>
<td>Liver</td>
<td>2%</td>
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</table>
Body mass index of OPMD patients compared to norms

- Compared with the mean BMI of 1912 Hispanic individuals age ≥49 yr in the 2011 National Health Interview Survey, the mean BMI of OPMD subjects was lower (25.3±5 vs 28.6±6, p<.001).
Conclusions

- OPMD patients have reduced body mass index compared with national averages.
- Adaptive equipment use is moderate (26% use some form of adaptive equipment for mobility), though prevalence of proximal weakness is high (83% had proximal lower extremity weakness).
- Lack of standardized assessments of disease severity hinders our ability to measure disease progression – such standardized assessments are necessary before we can plan clinical trials.
Future Directions

- Apply standardized measurements of disease severity as we follow patients longitudinally
- Identify outcome measures that best reflect disease progression
- Lay the groundwork to design good clinical trials of new treatments!!