TMA: Twenty Years Later – Progress in Understanding Myositis

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Major Advances in Myositis

- Better recognition of myositis and new diagnostic and assessment tools
- More understanding of the different types of myositis
- Identification of genes and possible environmental triggers
- New insights into how inflammation and damage develop
- New and improved treatments
- National and international networks working together to gain knowledge and improve treatment
- The Myositis Association’s critical role in patient, caregiver and physician education, patient support and advancing research in all areas above
Better Recognition of Myositis and New Diagnostic and Assessment Tools

- New autoantibody tests – over a dozen diagnostic autoantibodies discovered for PM/DM and recently for IBM (anti-cytoplasmic 5’nucleotidase)

- Better appreciation of muscle biopsy features/stains – rimmed vacuoles, MHC class I staining, others

- New imaging methods - particularly magnetic resonance imaging (MRI)

- New diagnostic genetic testing for non-myositis cases

- New validated and standardized clinical assessment tools for determining disease activity and damage and to define when patients improve
Different MRIs Show Disease Damage (T1) and Disease Activity (STIR)

T1 - MRI

STIR - MRI

Active DM

Active PM

Active IBM
Genetic Tests to Diagnose Mimics of Myositis

GENETIC LOCI FOR INHERITED MYOPATHIES

- Duchenne's MD (dystrophin)
- Becker's MD (dystrophin)
- Emory - Dreifus MD (emerin)
- Bethlem myopathy
- Central core myopathy (Ryanodine receptor)
- Myotonic (dystrophiny) (CTG repeats)
- Limb - Girdle MD 2D (adhalin)
- Limb - Girdle MD 2A
- Hypertrophic Cardiomyopathy (myosin)
- Limb - Girdle, MD 2C (Sarcoglycan)
- Phosphofructokinase deficiency
- Carnitine Palmitoyltransferase II
- Nemaline Rod Myopathy
- Miyoshi Distal myopathy
- FSH MD (dystroglycan)
- Limb Girdle MD 1
- Congenetal MD (Merosin)
- Fukuyama MD
- Inclusion body myopathy
- Mc Ardle's Disease
## The Broad Spectrum of Myositis

### By Diagnosis
- Polymyositis (PM)
- Dermatomyositis (DM)
- IBM
- Necrotizing myopathy
- Amyopathic DM
- Myositis in overlap
- Cancer and myositis
- Focal myositis
- Other

### By Autoantibody
- Negative
- Jo-1
- SRP
- Mi-2
- p155/140
- CADM-140
- MJ
- Cyto. 5’nucleotidase
- U1-RNP
- Other

### By Organ Involvement
- Skin
- Lung
- Esophagus
- Intestines
- Calcinosis
- Joints
- Heart
- Blood vessels
- Other

Courtesy Dr. Jiří Vencovský
Different Types of Myositis Have Different Problems and Treatment Responses

**PM**
- Moderate to severe weakness,
- Lung and heart disease,
- Moderately difficult to treat

**DM/JDM**
- Mild to moderate weakness,
- Calcium deposits, Ulcerations,
- Fat loss in skin,
- Better treatment responses

**Cancer Myositis**
- More DM and men,
- Severe weakness and rashes,
- Older age, Lower CK,
- Need to focus treatment on cancer

**IBM**
- More older males,
- Shoulder, wrist, hand and leg weakness,
- Asymmetry, atrophy, swallowing problems
Different Antibody Types Have Different Problems and Treatment Responses

**Anti-Jo-1**
- Lung disease, arthritis, fevers, persistent disease needing longer treatments

**Anti-SRP**
- Acute, severe weakness, swallowing problems, muscle pain, more difficult to treat

**Anti-Mi-2**
- Classic dermatomyositis, V-sign & shawl rashes, good response to treatment
Different Juvenile DM Antibody Types Have Different Problems and Responses

**Anti-p155/140**

Severe skin rash, moderate to severe weakness, difficult to treat and chronic disease

**Anti-MJ**

Muscle cramps, calcium deposits, GI ulcers, easier to treat and single course of disease

**Myositis Autoantibody Negative**

Joint pains, fever, lower CK, easier to treat and single course of disease
Genes Differ in Different Myositis Types

- Immune genes that normally protect us from environmental agents are the most important genes in myositis (called HLA genes).
- PM, DM, and IBM all share some HLA genes, but also each has unique risk or protective HLA genes.
- Different autoantibody groups also have different genes.
- New approaches to evaluate genes across the entire human genome are finding additional genes for myositis that may help in diagnosis and treatment in the future.
Possible Environmental Triggers of Myositis

- **Infections**
  - Viruses: Echovirus, HIV, Coxsackievirus, Hepatitis, others
  - Bacteria: Group A Streptococcus, Lyme, others
  - Parasites: Toxoplasma, others

- **Non-Infectious agents**
  - Drugs: D-penicillamine, growth hormone, cytokines, cimetidine, estrogens, statins, others
  - Foods: L-tryptophan, dietary supplements, ciguatera toxin, others
  - Occupational exposure: Silica, super glues, others
  - Other environmental exposures: Collagen implants, smoking, overexertion, stress, sunlight, others
Sunlight Levels Predict the Proportion of Dermatomyositis World-wide and in the U.S.

![Graph showing the correlation between sunlight levels and percentage of dermatomyositis patients.](image)

- N = 919, $R^2 = 0.9$, $P < 0.0000001$
Possible Ways that Inflammation and Damage Develop in Myositis

Environmental Risk Factors Interact With Genetic Risk Factors

Immune Activation, Cytokine release, Autoantibody Production

Dermatomyositis
Juvenile Dermatomyositis

Polymyositis
Inclusion Body Myositis

Tissue Inflammation and Damage

Tissue Repair
## New Treatment Options and Understanding the Need for More Aggressive Therapy

<table>
<thead>
<tr>
<th>Primary Therapy</th>
<th>Oral or IV Corticosteroids</th>
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<tbody>
<tr>
<td><strong>First Line Adjuncts</strong></td>
<td><strong>Physical &amp; Occupational Therapy</strong></td>
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<td>For DM:</td>
<td>Sun precautions</td>
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New Treatment Options and Understanding the Need for More Aggressive Therapy

<table>
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<tr>
<th>Second Line Therapies (First line for poor prognosis)</th>
<th>Bolus IV Corticosteroids</th>
<th>Methotrexate</th>
<th>Azathioprine</th>
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<tr>
<td></td>
<td>Intravenous Gammaglobulin (IVIG)</td>
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<td></td>
<td>Cyclosporine</td>
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<thead>
<tr>
<th>Third Line Therapies</th>
<th>Tacrolimus</th>
<th>Mycophenolate</th>
<th>Acthar</th>
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<tr>
<td></td>
<td>Cyclophosphamide</td>
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<td>Rituximab</td>
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| Combination Therapies                            |            |               |               |

| Experimental Therapies                           | BAF312 to block immune cell movement in PM | BYM338 (bimagrumab) to block myostatin/activin in IBM | Follistatin (FS344) gene therapy to block myostatin in IBM | Autologous stem cell transplantation in PM/DM |
More International Networks/Collaborations

- International Myositis Assessment and Clinical Studies Group (IMACS)
- The International Myositis Collaborative Study Group
- International Myositis Genetics Consortium (MYOGEN)
- EuroMyositis
- Paediatric Rheumatology International Trials Organisation (PRINTO)
- International Myositis Classification Criteria Project (IMCCP)
- Childhood Arthritis and Rheumatology Research Alliance (CARRA)
TMA’s Major Impact on Myositis

Education and support
- Thousands of patients, caregivers and family members have a better understanding of their disease and know that others are there to help them
- Hosted many patient meetings
- Established September 21st as National Myositis Awareness Day
- Published books and other information

Fostered Research
- Hosted many scientific meetings to enhanced understanding, and advanced research into the causes and treatments of all forms of myositis
- 34 research grants approved for a total of $4.2 million
- At least 50 publications in the medical literature supported by TMA
- Currently playing an active direct role in research - MYOVISION
A registry of ~2000 patients diagnosed with adult and juvenile DM, PM, IBM and other rarer forms of myositis

Data collected through paper and online surveys

Only patients residing in the United States or Canada at the time of onset were eligible

Joint collaboration between NIEHS Environmental Autoimmunity Group, The Myositis Association and the Cincinnati Children’s Hospital Medical Center
MYOVISION GOALS

- Establish a myositis patient registry to investigate:
  - Demographics
  - Manifestations of illness
  - Treatments
  - Medications received
  - Types of physicians involved in care

- Investigate potential environmental exposures related to onset of disease

- Evaluate impact of disease on quality of life

- Examine additional exploratory research questions related to environmental risk factors

- Create a population resource that can be re-contacted for future studies
Summary - Major Advances in Myositis

- Over the last twenty years there have been many advances in diagnosis, disease assessment, understanding the types of myositis, how they come about and how to best treat them.
- The Myositis Association has played a critical role in patient, caregiver and physician education, patient support and advancing research in all of the above areas.
- Much more needs to be done to understand the causes and best treatments for each type of myositis, to find cures, and to eventually prevent the development of myositis in the future.