JUVENILE DERMATOMYOSITIS
- how to diagnose, how to treat?

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Juvenile Dermatomyositis

- Rare, serious systemic autoimmune disease
- Immune occlusive small-vessel vasculopathy
- The most common juvenile idiopathic inflammatory myopathy – JIIM (~85%)
- Skin, skeletal muscles, joints, GIT, heart, lungs
- 1-5% amyopathic JDM (of these, ~25% develop overt JDM)
- ~1/3 have acute, monocyclic course (up to 2 years)
- ~1/4 have polycyclic disease
- Chronic, continuous disease in >50%
- Even after >16 years of evolution, >50% of JDM patients still have an active disease (capillary nailfold changes, skin rash...)


Before the steroid era:
- 1/3 died
- 1/3 significant disability
- 1/3 completely recovered

Today:
- mortality rate <2%

Generally, not paraneoplastic. Very rare paraneoplastic cases described (~1%)

JDM, demographic data

Incidence

- US, UK: \( \sim 3 / 1,000,000 \) children/year
- World: \( 1 - 4 / 1,000,000 \)

Gender

- World - Girls : Boys \( \sim 3 : 1 \)
- India - Girls : Boys \( = 1 : 1.7 \)
- Japan - Girls : Boys \( = 1 : 1.3 \)
JDM, demographic data

Age at onset

– Bimodal
  - peak I: 2-5 years
  - peak II: 12-13 years

– USA: median age at onset 7.5 – 10.8 years

– World: mean age at onset ~7 years
JDM, genetic data

- Complex interplay:
  - Immunological dysfunction (genetic background)
  - Environmental stimuli / triggers (infection, drugs, UV light...)

- Inflammatory myopathies: complex polygenic disorders
  - Identification of specific loci hampered by the rarity of JDM

- HLA-B*08, DRB1*0301, and DQA1*0501, for white adults and children with DM in USA and Europe

- Also, HLA-DPB1*0101 and DQA1*0301 – additional risk for JDM

- HLA-DRB1*1501 in patients with monocyclic disease (22%)

- Strong association between specific risk alleles and the serological phenotype

JDM, genetic data

- TNFa-308A allele carriers produce more thrombospondin-1:
  - Intimal hyperplasia
  - Luminal narrowing
  - Vascular occlusion
  - Increased TNFa production

- TNFa-308A allele also associated with:
  - Prolonged disease course
  - Calcinosis
  - Partial lipodystrophy
  - Ulcerations
Humoral immunity

- Up to 70% JDM patients have autoantibodies

- **Myositis-Specific Abs (MSA)** – only in (J)DM
  - anti-ARS (Jo1, OJ, EJ...), anti-SRP, anti-Mi2...

- **Myositis-Associated Abs (MAA)** – present also in other diseases
  - anti-PM-Scl, anti-U1-RNP, anti-Ku...

- Defined subsets of JIIM; important for prognosis

- Antigenic targets: cytoplasmic or nuclear proteins involved in:
  - protein synthesis (e.g. tRNA-synthetase enzymes)
  - gene regulation
Some antibodies have the same associations as in adults:

**anti-PM-Scl:**
- overlap with scleroderma

**anti-Mi-2:**
- classic skin rash
- milder muscle involvement
- lower risk of interstitial pneumonia
- respond well to therapy

**anti-Jo-1:**
- interstitial lung disease
Humoral immunity

- Some differences in JDM autoantibody profile:
  - anti-p155/140 (in 23-35% JDM patients): increased risk of skin disease, prolonged course
  - anti-p140: risk of calcinosis

- Do these antibodies predate the specific features?

- Prognosis

- Specifically targeted therapy

# Myositis-Specific Abs and Myositis-Associated Abs in Juvenile Idiopathic Inflammatory Myopathies (JIIM) (JDM, JPM, juvenile CT disease myositis)

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Clinical associations</th>
<th>JIIM group</th>
<th>Frequency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antisynthetases</strong> <em>(e.g. anti-Jo1)</em></td>
<td>Fever, Raynaud, arthritis, lungs</td>
<td>JPM, <strong>JDM,</strong> JCTM</td>
<td>2-4%</td>
</tr>
<tr>
<td><strong>Anti-Mi2</strong></td>
<td>Classic DM rash, mild disease, Hispanics</td>
<td><strong>JDM,</strong> JCTM</td>
<td>2-13%</td>
</tr>
<tr>
<td><strong>Anti-p155/140</strong></td>
<td>Ulcerations, severe photosensitive rash, lower CK, chronic dis. (adults: neo)</td>
<td><strong>JDM,</strong> JCTM</td>
<td>23-35%</td>
</tr>
<tr>
<td><strong>Anti-MJ</strong></td>
<td>Dysphonia, calcinosis, monocyclic disease</td>
<td><strong>JDM</strong></td>
<td>23-25%</td>
</tr>
</tbody>
</table>

- Endothelial dysfunction important in JDM
  - Fundamental in most devastating complications

- Capillary loss – early change, associated with poorer prognosis

- Ab deposition and complement activation on small vessels

- Cytokines and chemokines (IL-1, ICAM-1, CXCL10...) propagate the inflammation
Depletion and dilatation of the remaining capillaries

Dermatomyositis  Normal
Innate immunity – DC, MC

- Mature dendritic cells found in muscles
- Mature DC and mast cells present in involved and uninvolved skin in JDM patients
- DC and MC capable of driving the type I interferon response

Early pathological changes in JDM and adult DM

- Maturation of dendritic cells to mature plasmacytoid dendritic cells
- Strong type-1 IFN response
- Inflammatory response in muscles - upregulation of HLA I and type 1 IFN inducible genes
- Migration of lymphocytes through the vascular space promoted by upregulation of adhesion molecules ICAM, VCAM; MAC
- Trafficking of DC - upregulation of chemokine receptors 3 and 4, tissue factor (CD142)...
- Upregulation of lymphoid neogenesis markers chemokine 19 and 21
- Hypoxia in muscles damages endothelial cells, upregulates HLA I and endoplasmic reticulum chaperones
- The stress response ER - DNA damage
Perifascicular atrophy in muscles
BOHAN AND PETER CRITERIA FOR THE DIAGNOSIS OF DERMATOMYOSITIS

Individual criteria:
1. Symmetric proximal muscle weakness
2. Muscle biopsy evidence of myositis
3. Increase in serum skeletal muscle enzymes
4. Characteristic electromyographic pattern
5. Typical rash of dermatomyositis

Dermatomyositis:
Definite: 5 plus any 3 of 1-4
Probable: 5 plus any 2 of 1-4
Possible: 5 plus any 1 of 1-4

JDM, diagnosis

- In children, difficult to accomplish:
  - EMG
  - Muscle biopsy

- Today, common practice to forgo EMG and biopsy

- Noninvasive diagnostic methods:
  - Myositis autoantibodies
  - MRI
MRI in diagnosis of JDM

MRI in JDM

- Abnormalities specific for JDM found in:
  - 91% patients examined by MRI
  - 50% patients examined by EMG
  - 76% of muscle biopsies

- False-negative findings:
  - In 50% of JDM patients examined by EMG

- MRI scoring system (gluteal, thigh muscles)

- Whole-body MRI (forearm and lower-leg lesions, clinically underrecognized)

JDM, Dept Dermatology, Belgrade
January 1990 - December 2016 (27 years)

- 15 children, 12 girls + 3 boys (4 : 1)
- 379 adult DM patients (278 F : 101 M = 2.75 : 1)
  - JDM ~25x less frequent (3.8% of all DM cases)
- Age at onset 7 years (3.5 to 13)
- 5 months (2-10) between symptoms and dg
- Complaints at initial presentation:
  - 13 (87%) “rash”
  - 9 (60%) arthralgias, myalgias
  - 7 (47%) weakness alone
  - 7 (47%) presented to a dermatologist first
- 7/15 (47%) had a preceding infection
JDM, Belgrade, 1990-2016

Initial physical examination

- 15 (100%) periungual erythema, telangiectases
- 13 (87%) Gottron’s papules
- 12 (80%) periorbital heliotrope rash
- 12 (80%) red, scaly plaques on elbows/knees
- 8 (53%) malar erythema
- 7 (47%) pruritus
- 5 (33%) hypertrophic and ragged cuticles
- 3 (20%) livedo reticularis
- 2 (13%) skin ulcerations
- 2 (13%) mechanic’s hands
Localized poikiloderma
Generalized poikiloderma
Lipodystrophy (focal)
Lipodystrophy (generalized)

2008, age 14

2014, age 20
JDM, 1990-2016
Musculoskeletal examination, Antibodies

- 13 (87%) decrease in quadriceps strength
- 9 (60%) decrease in deltoid strength
- 3 (20%) synovitis
- 15 (100%) elevated LDH
- 11 (73%) elevated CK
- 11 (73%) elevated AST
- 10 (67%) inflammatory myopathy on EMG
- 11 (73%) significant ANA titer
- 6/10 (60%) had MSA and MAA
  - (4 Mi-2, 2 PM-Scl, 1 Ku)
JDM, Belgrade, 1990-2016

**Therapy**

- **15** received prednisone at 1-2 mg/kg
  - 3/15 - in some phases - pulsed iv methylprednisolone
- **10** – methotrexate
- **2** – IVIg
- **15** - chloroquine or hydroxychloroquine
- **15** – physiotherapy
- Photoprotection, vit D + Ca supplementation
JDM, 1990-2016

Outcome

- No deaths
- 4 (27%) calcinosis (3 mild, 1 severe)
- 8 (57%) monocyclic course (<2 years)
- 6 (43%) polycyclic/chronic course
- 1 underetermined (JDM duration <1.5 yrs)
JDM therapy

- Marked mortality reduction after the introduction of corticosteroids (CS)

- CS + MTX = reduction of CS use
  - (from 27 to 10 months)

- azathioprine vs. MTX - no significant difference

- cyclosporine vs. MTX - no significant difference
JDM therapy

First line

- **Corticosteroids**
  - oral prednisone 2 mg/kg
  - or pulse intravenous methylprednisolone, 30 mg/kg/d (3-5 days) for more severe disease, followed by oral prednisone

- **Methotrexate** (+ folic acid 1-5 mg p.o.)
  - oral or subcutaneous 0.4-1 mg/kg or 15-20 mg/m² weekly, maximum 40 mg
  - to be continued for at least 1 yr after achieving remission

- **Intravenous immunoglobulin (IVIg)**
  - 2 g/kg, maximum 70 g, in 1 or 2 days, monthly, in refractory or severe disease
JDM therapy
Second line

- Cyclosporine
- Azathioprine
- Tacrolimus
- Mycophenolate mofetil
- Rituximab
  - 83% of refractory adult and juvenile patients reached the definition of improvement
  - But, the response was slow
  - anti-Jo1 and anti-Mi2 were the strongest predictors for quicker response

## Biologics in JDM

### Table 1 Biologic agents currently used in juvenile myositis

<table>
<thead>
<tr>
<th>Medication</th>
<th>Mode of action</th>
<th>Administration</th>
<th>Doses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abatacept</td>
<td>Humanised selective T-cell co-stimulatory modulator</td>
<td>IV infusion over 30 min</td>
<td>10 mg/kg at 0, 2, 4 weeks, then every 4 weeks, max. dose 1 g</td>
</tr>
<tr>
<td>Adalimumab</td>
<td>Humanised soluble anti-TNF monoclonal antibody</td>
<td>SC</td>
<td>24 mg/m² up to 40 mg every 2 weeks</td>
</tr>
<tr>
<td>Infliximab</td>
<td>Chimeric human-murine anti-TNF IgG1 monoclonal antibody</td>
<td>IV infusion</td>
<td>6 mg/kg at 0, 2, 6 weeks, then every 4–8 weeks according to response</td>
</tr>
<tr>
<td>Rituximab</td>
<td>Chimeric anti-CD20 monoclonal antibody</td>
<td>IV infusion</td>
<td>750 mg/m² on days 0–14 (given with 100 mg methylprednisolone and often cyclophosphamide)</td>
</tr>
</tbody>
</table>
| Tocilizumab     | Humanised recombinant anti-IL-6 receptor monoclonal antibody | IV infusion | BW \( \geq 30 \text{ kg} \): 8 mg/kg once every 2 weeks  \\
|                 |                                                      |                      | BW \( <30 \text{ kg} \): 12 mg/kg once every 2 weeks               |

JDM therapy
Third line

- Cyclophosphamide
- Janus kinase (JAK) inhibitors
- Autologous stem-cell transplant
JDM therapy
Adjunct measures

- Sunscreens (SPF 50+) and sun avoidance
- Topical corticosteroids, tacrolimus, pimecrolimus
- Hydroxychloroquine
  - 5 mg/kg/day
- Ca and vitamin D - osteoporosis prevention
Calcinosis (15-50% of JDM patients)

- **Bisphosphonates**
  - Etidronate
  - Pamidronate
    - 1 mg/kg/day, iv, on 3 consecutive days, every 3 months

- **Thalidomide** (TNF modulator)

- **Surgical excision**

After 6 months

- pulsed iv methylprednisolone +
- MTX po
After 6 months

- pulsed iv methylprednisolone +
- MTX po
After 6 months

- pulsed iv methylprednisolone +
- MTX po
Juvenile Dermatomyositis

- A rare disease
- Early recognition and adequate therapy
- Prevention of calcinosis, disability
- Lipodystrophy and calcinosis remain difficult issues
- Prognosis better than in adult DM
- Mortality rate nowadays <2%
- Increased risk of cardiovascular disease in adulthood?
- New therapies emerging
- New collaborative studies necessary to answer further questions
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Big thanks to my collaborators!
Greetings from Belgrade!

Thank you for your attention!