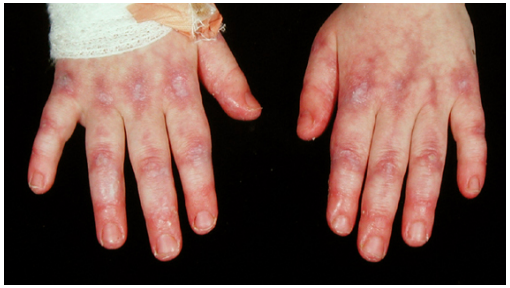
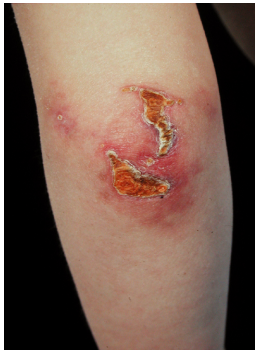




Dermatomiositis juvenil
Juvenile dermatomyositis

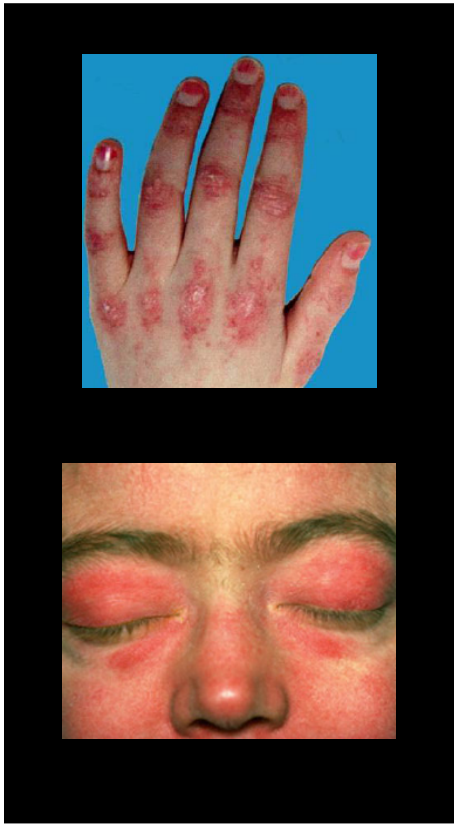
Lucy R Wedderburn

UCL Institute of Child Health and

Great Ormond Street Hospital

London UK

Dermatomyositis



Bohan and Peter NEJM, 1975

- Characteristic rash,
- with other criteria:
  - Proximal muscle weakness
  - Raised serum muscle enzymes
  - Typical changes in muscle biopsy
  - Typical changes on EMG

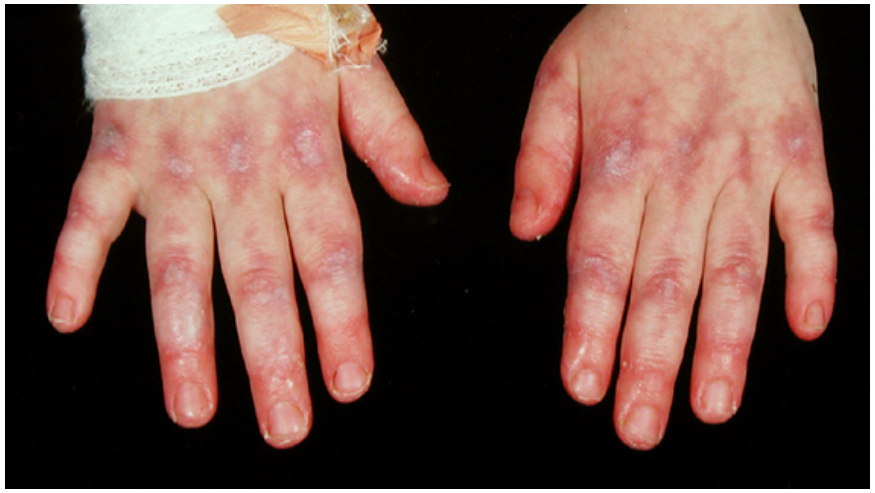
- 3 or 4 criteria - definite DM
- 2 criteria - probable DM
- 1 criterion - possible DM

Problems with B& P criteria :

- Brown et al, 2006, Rheumatology
- IMACS working group

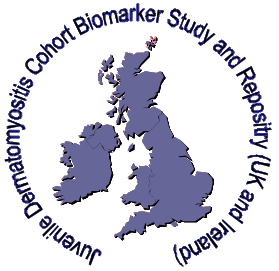
Juvenile Dermatomyositis

- The most common IIM of childhood
- Incidence 2 - 4 per million/year
- 2.2 :1 F:M ratio
- Mean age onset 7 years (4 -10)



UK JDM Cohort and Biomarker study and Repository

- 2000 Juvenile Dermatomyositis Research Centre UCL ICH
- Now called Juvenile Dermatomyositis Cohort Study
- UK Juvenile Dermatomyositis Research Group (JDRG)
- 12 centres involved
- Clinical / laboratory information, samples, at diagnosis and 6 monthly for 2 years then annually
- Biobank of cells, DNA, serum, plasma, biopsy material
- 365 children recruited
- McCann et al Rheumatology 2006
- Martin et al, Rheumatology 2011



http://www.juveniledermatomyositis.org.uk/

Login: Password: Go

JDRG
Juvenile Dermatomyositis Research Group

Juvenile Dermatomyositis Cohort Biomarker Study and Repository UK & Ireland

- Home
- What is JDM
- Treatment
- About JDRG
- Research
- Patients / Parents
- Charitable Fund
- Meetings
- Contact
- Links
- Website Feedback

Contact us for details:
Juvenile Dermatomyositis Research Centre
Institute of Child Health
University College London
30 Guilford Street
London UK
WC1N 1EH
Email: info@jdrg.org.uk
Fax: 0207 905 2672

Welcome to JDRG

Juvenile Dermatomyositis (JDM) is an illness of children which affects the skin (dermato) and muscles (myositis) and frequently other parts of the body including joints, lungs, gut and blood vessels. See Treatment.

As JDM is a rare condition, (affecting about 3 children in a million each year in the UK) this makes it very difficult to carry out research.

In 2000 a group of leading UK Rheumatologists formed The Juvenile Dermatomyositis Research Group (JDRG) and began recruiting patients to the JDM Cohort Biomarker Study and Repository (formally known as the National (UK and Ireland) Registry and Repository). See About JDRG

The study and repository collects and stores serial clinical data linked to biological specimens such as blood, serum, DNA, skin and muscle tissue from biopsies. The data and specimens facilitate research into JDM and other forms of myositis. See Research The resource is open to project applications from clinicians, scientists and researchers. All applications are controlled by an independent steering committee to secure the quality of the research conducted.

Muscle assessment in children with myositis

Proximal muscles initially

Clinical tools:

Childhood Myositis Assessment Scale (CMAS): 14 items, measures strength, function and endurance; takes about 10 min to complete; Lovell et al A&R 1999. Validated; Huber et al A&R 2004

Manual Muscle testing (MMT8): 8 groups of muscles, each out of 10 , total score 0-80; Rider et al Arth C and Res 2010

Imaging: MRI widely used

ARTHRITIS & RHEUMATISM
Vol. 42, No. 10, October 1999, pp 2213–2219
© 1999, American College of Rheumatology

DEVELOPMENT OF VALIDATED DISEASE ACTIVITY AND DAMAGE INDICES FOR THE JUVENILE IDIOPATHIC INFLAMMATORY MYOPATHIES

II. The Childhood Myositis Assessment Scale (CMAS): A Quantitative Tool for the Evaluation of Muscle Function

DANIEL J. LOVELL, CAROL B. LINDSLEY, ROBERT M. RENNEBOHM, SUSAN H. BALLINGER, SUZANNE L. BOWYER, EDWARD H. GIANNINI, JEANNE E. HICKS, JOSEPH E. LEVINSON, RICHARD MIER, LAUREN M. PACHMAN, MURRAY H. PASSO, MARIA D. PEREZ, ANN M. REED, KENNETH N. SCHIKLER, MICHAELE SMITH, LAWRENCE S. ZEMEL, and LISA G. RIDER, in cooperation with THE JUVENILE DERMATOMYOSITIS DISEASE ACTIVITY COLLABORATIVE STUDY GROUP

Arthritis Care & Research
Vol. 62, No. 4, April 2010, pp 465–472
DOI 10.1002/acr.20035
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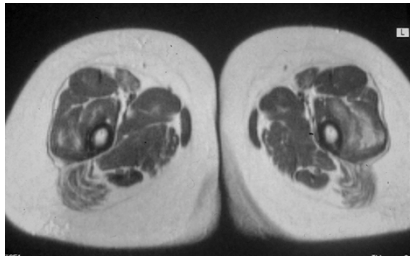
ORIGINAL ARTICLE

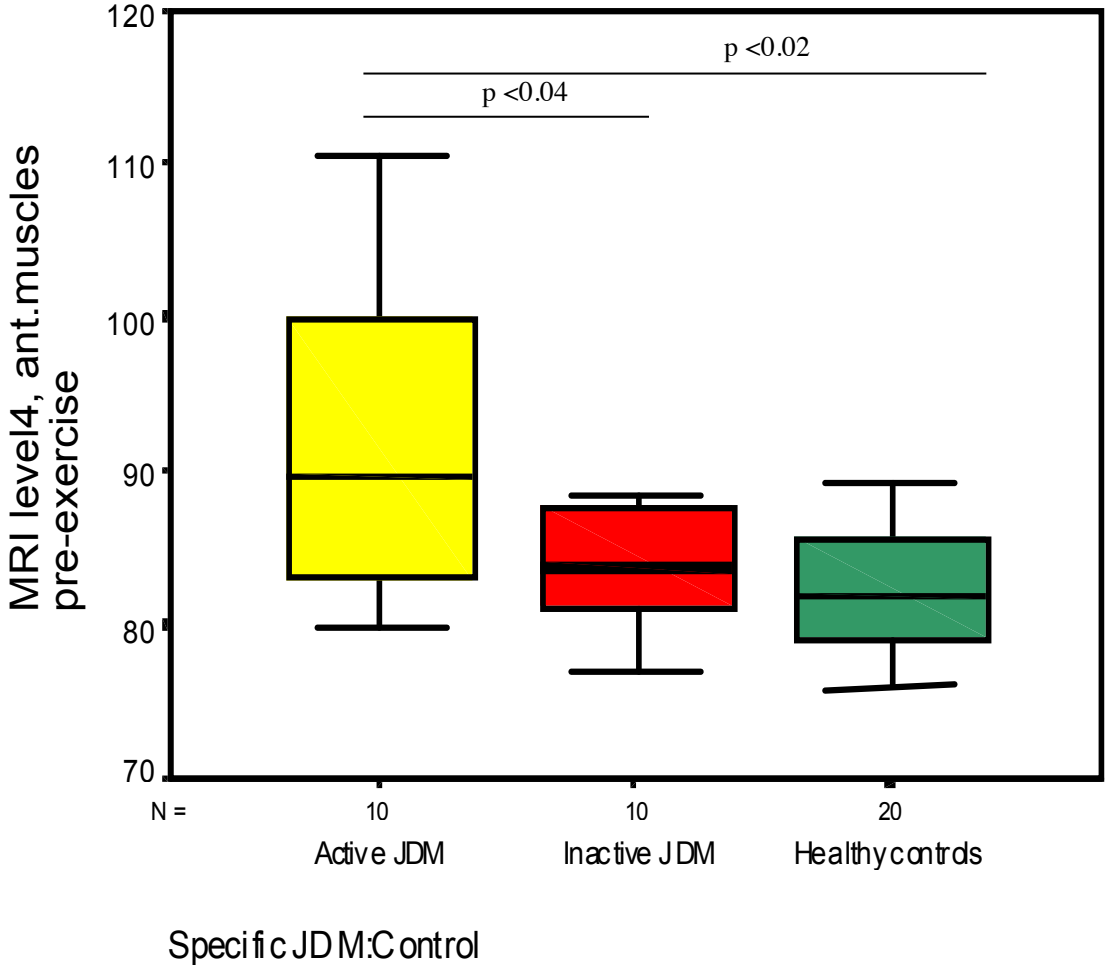
Validation of Manual Muscle Testing and a Subset of Eight Muscles for Adult and Juvenile Idiopathic Inflammatory Myopathies

LISA G. RIDER,[1] DELORIS KOZIOL,[2] EDWARD H. GIANNINI,[3] MINAL S. JAIN,[2] MICHAELE R. SMITH,[2] KRISTI WHITNEY-MAHONEY,[4] BRIAN M. FELDMAN,[4] SUSAN J. WRIGHT,[5] CAROL B. LINDSLEY,[5] LAUREN M. PACHMAN,[6] MARIA L. VILLALBA,[7] DANIEL J. LOVELL,[3] SUZANNE L. BOWYER,[6] PAUL H. PLOTZ,[7] FREDERICK W. MILLER,[1] AND JEANNE E. HICKS[2]



Quantitative assessment on MRI

MRI T2 weighted relaxation time



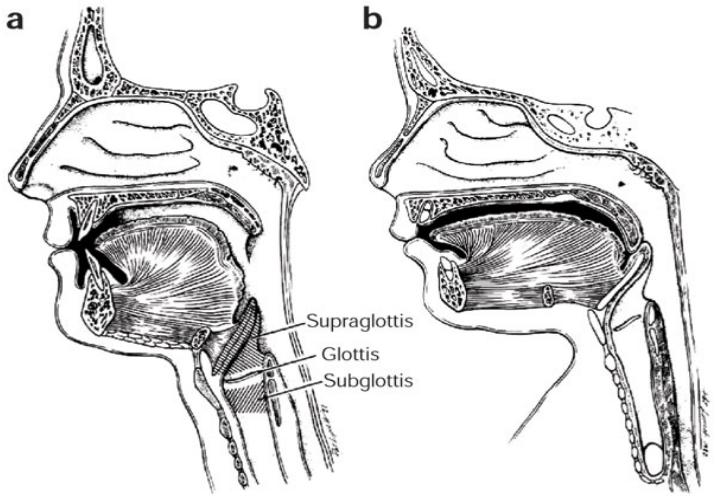
Maillard et al 2004, 2005

Skin assessment in children with myositis

- Eyes heliotrope rash
- Extensor surfaces – Gottrons
- Photosensitivity
- Ulceration
- Calcinosis
- Nails: capillaroscopy

Other clinical aspects of juvenile myositis

- Fever
- Anorexia
- Oedema
- Lipodystrohpy
- Arthritis
- Raynaud's
- Speech /swallow problems
- Voice changes
- Respiratory problems
- Cardiac
- GI symptoms



Disease assessment in DM :

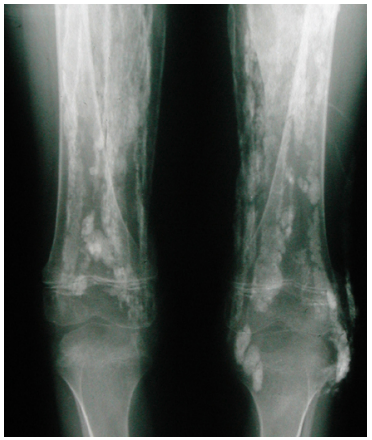
Activity and damage core sets: PRINTO, IMACS

Physician	Global score VAS
Patient/parent	Global score VAS
Strength	MMT, CMAS
Function	CHAQ
Muscle enzymes	CK, ALT, AST, LDH, aldolase
Extra-muscular disease	DAS, MDAA

Miller et al, 2001
Ruperto et al 2003
Isenberg et al 2004

JDM differs from adult DM

- Not associated with cancer
- Complications : vasculitis, ulceration, calcinosis
- CNS and gut involvement
- More overlap with other conditions such as scleroderma



JDM modern management

- Early aggressive treatment:
- High dose steroids: iv MP then oral Pred (1-2mg/kg) and tapering
- Early use of subcutaneous methotrexate (MTX), 15mg/m2
- Some use iv Immunogloubulin, cyclosporin, MMF
- Cyclophosphamide for severe cases, Riley et al 2004
- Use of Biologics : Etanercept, Infliximab, Riley et al 2008
- Rituximab (anti CD20)
- ACST – case reports
- Multi- disciplinary team approach

What is the evidence base for current practice ?

JUVENILE DM

MTX + iv/oral Pred reduces steroid dose
Huang et al1999, Miller et al1992, Ramanan et al, 2005

Consensus on moderate-severe JDM protocols: iv MP then oral Pred (2mg/kg/d) with MTX (sc) Huber et al, 2010

Other DMARDS : Cyclosporin A, ivIg, MMF:
All reported in case series, small studies

Cyclophosphamide 30mg/kg severe 12 cases *Riley* et al, *2004*

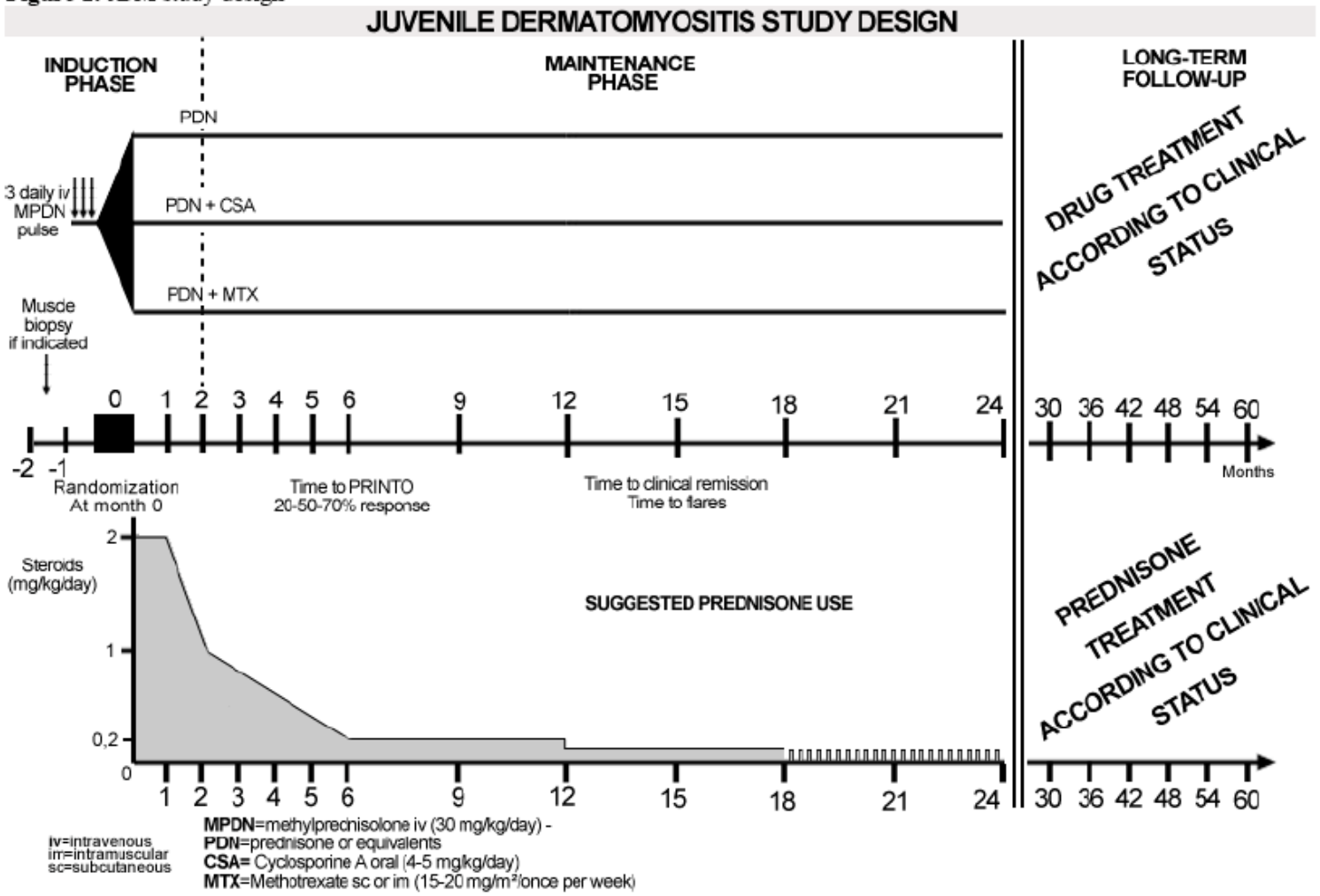
anti TNF: Infliximab 5 cases, *Riley* et al, *2008*

Rituximab, Other biologics, ACST….. cases

PRINTO study JDM

Single blind Phase III Randomised Controlled Clinical Trial in new onset JDM

Figure 1: JDM study design



Consensus based protocols

Arthritis Care & Research
Vol. 62, No. 2, February 2010, pp 219–225
DOI 10.1002/acr.20071

ORIGINAL ARTICLE

Protocols for the Initial Treatment of Moderately Severe Juvenile Dermatomyositis: Results of a Children's Arthritis and Rheumatology Research Alliance Consensus Conference

ADAM M. HUBER,[1] EDWARD H. GIANNINI,[2] SUZANNE L. BOWYER,[3] SUSAN KIM,[4] BIANCA LANG,[1] CAROL B. LINDSLEY,[5] LAUREN M. PACHMAN,[6] CLARISSA PILKINGTON,[7] ANN M. REED,[8] ROBERT M. RENNEBOHM,[9] LISA G. RIDER,[10] CAROL A. WALLACE,[11] AND BRIAN M. FELDMAN[12]

And Huber et al 2011; Arthritis Care & Research DOI 10.1002/acr.20695

JDM : long term outcome data

PRINTO study

- 490 cases JDM, mean disease duration 7.7 yr
- 58.7% chronic or polycyclic course, 3% mortality
- 41.2 % had ongoing muscle weakness
- 41.2 % had persistently active disease *Ravelli et al 2010*

IMACS study

- 143 JDM, 96 adult DM, assessment using the MDI *Isenberg 2004*
- Disease duration 6.8 years
- 79% JDM damage; 97 % adult *Rider et al 2009*

What causes muscle weakness in JDM?

Muscle biopsy in JDM

- B and P criteria still include muscle biopsy

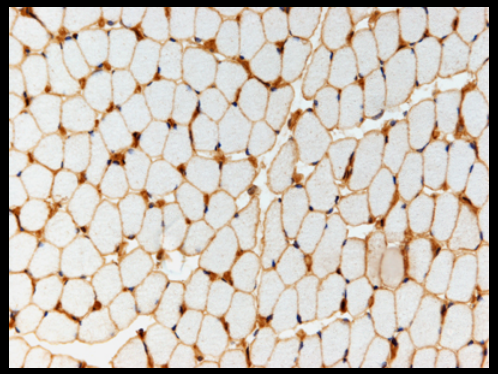
- Minority of JDM patients have biopsy done
- 20% early JDM biopsies reported as ‘normal’

- Many features may be reported upon
- No validated method or tool with which to quantify abnormality
- No validated data on how pathological features relate to disease course, response to Rx, outcome

JDM weak muscle is abnormal before there is any inflammatory infiltrate

MHC class I expression

JDM



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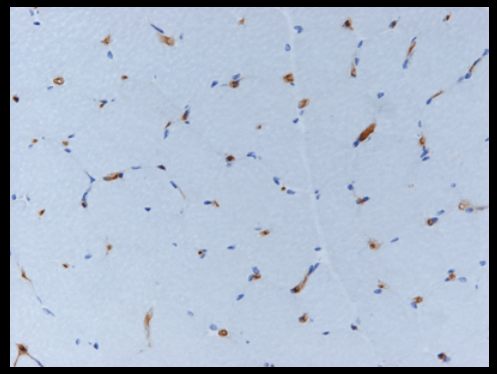
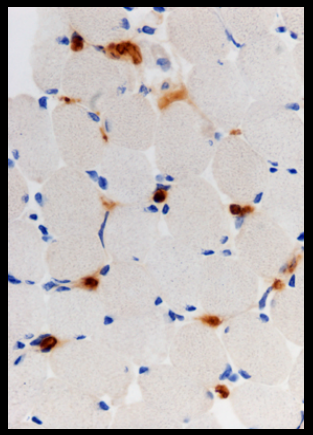


Li et al 2004

C5-9 deposition

JDM



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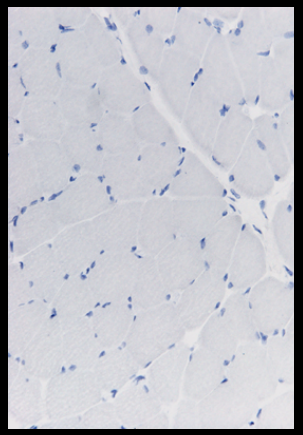
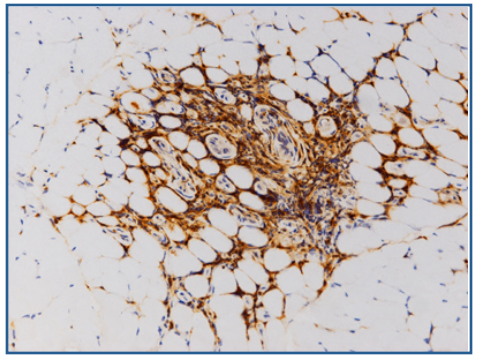
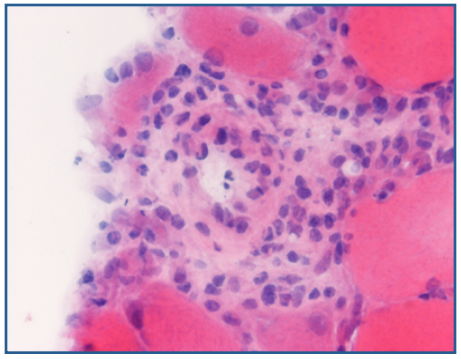
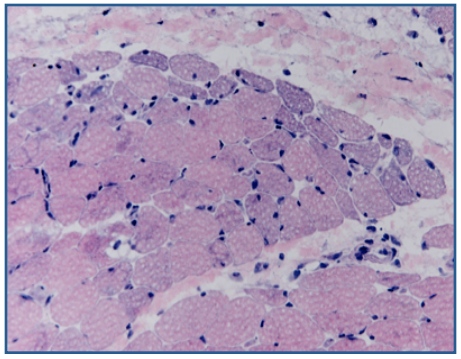
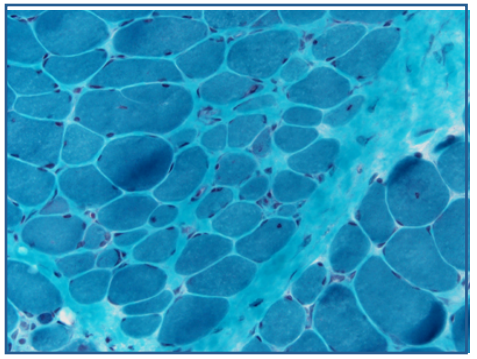


Varsani, H. 2007

JDM muscle biopsy study

International JDM biopsy working group

Samples from UK JDM Repository

Four domains : each with many items, each carefully defined

1. **Inflammatory**
2. **Vascular**
3. **Muscle Fibre**
4. **Connective Tissue**

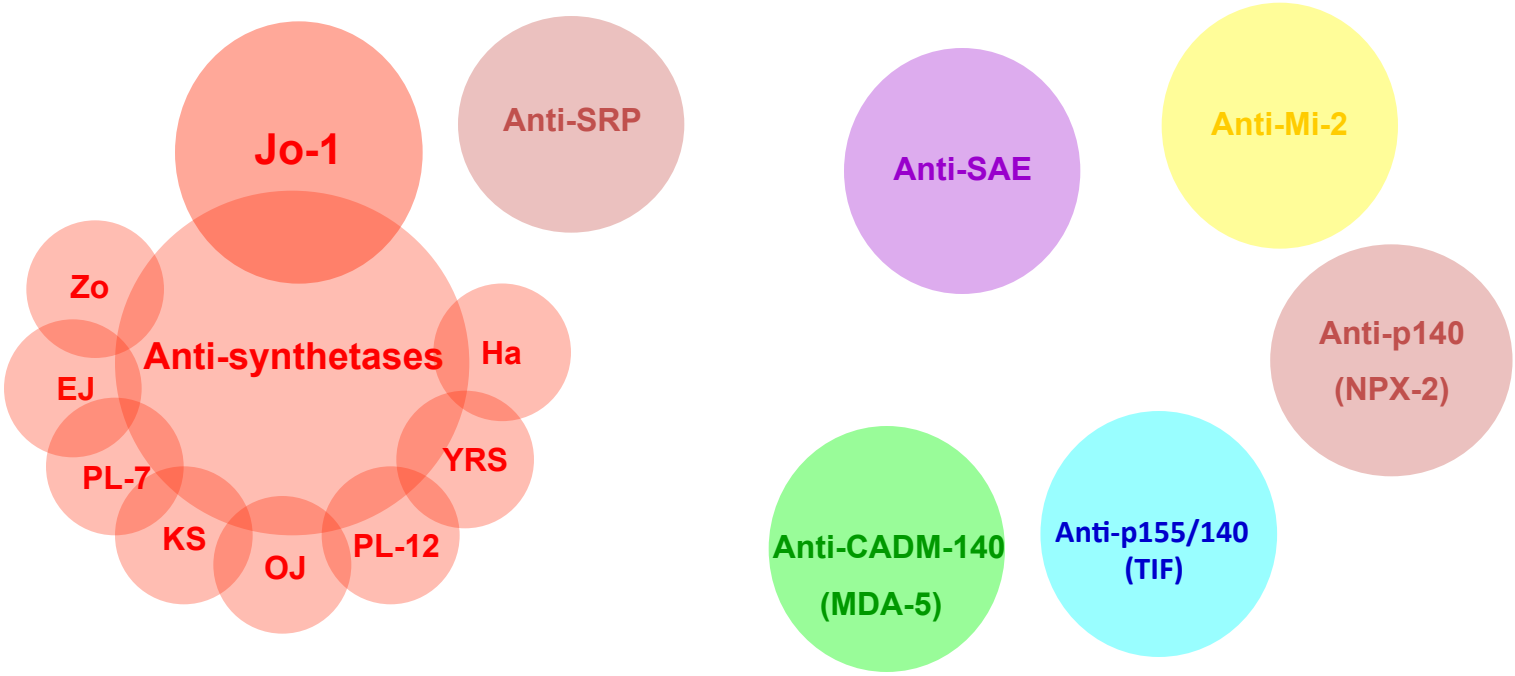
MYOSITIS SUPPORT GROUP
Registered Charity No.327791

Visual analogue scale, VAS (0-10)

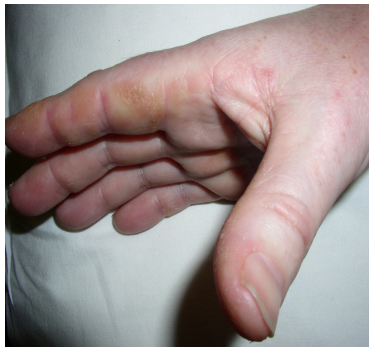
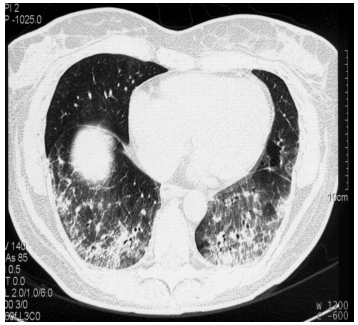
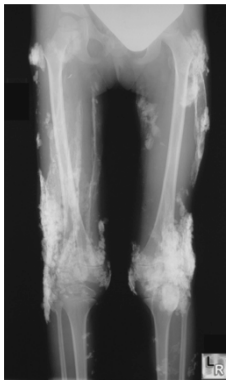
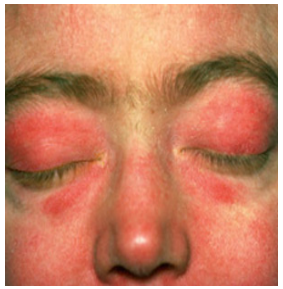
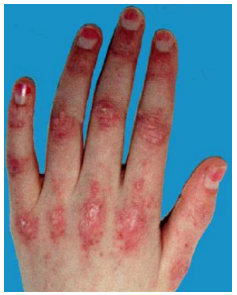
normal 0 ——— 10 not normal

Wedderburn et al, A and R 2007

Autoantibodies in adult and juvenile myositis



Myositis specific autoantibodies → Clinical phenotypes in adults and children

1. Gunawardena H *et al*. Curr Opin Rheum 2008
2. Gunawardena H *et al*. Rheumatology 2009

Novel autoantibodies in JDM

- ~75% patients with JDM are ANA+
- Low frequency of anti-synthetase autoantibodies eg Jo-1 (1-3%)
- 162 children from JDM Cohort Study
- Antibodies defined using immunoprecipitation
- Autoantibody profiles matched to clinical data eg antiMi-2 classic MD/JDM rash

- Two major new autoantibodies defined:
  - Anti-p155/140
  - Anti-p140
  - Mutually exclusive
  - Target different autoantigens

Wedderburn et al, Rheumatology 2007

Novel autoantibodies in JDM : anti- p155/140

- 17% of UK JDM cases (n=162)
- more severe skin rash
- Adults : strong association with cancer meta analysis Selva-O'Callaghan A, 2010
- No malignancy to date in JDM

- Target antigens : transcriptional intermediary factor TIF;
- TIF1γ (TRIM33)/TIF1α (TRIM24)
- E3 ligases; ubiquitin pathway
- Implicated in epigenetic changes

Gunawardena H, et al, Rheumatology 2008

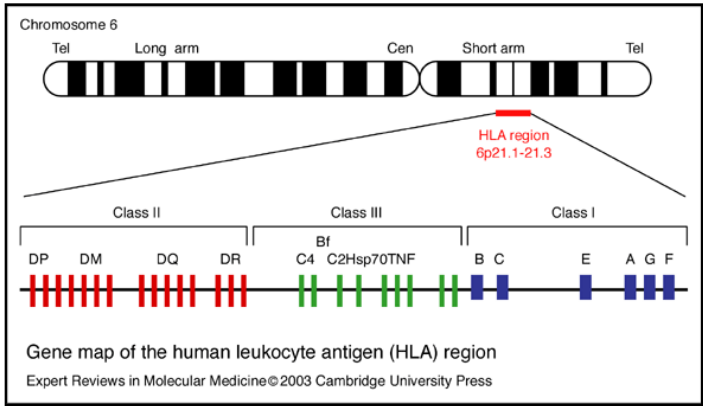
Novel autoantibodies in JDM : anti- p140

- Anti p140 (anti MJ):
- Target antigen transcription factor NPX-2
- 23% JDM UK cohort
- Higher risk of calcinosis
- 5% adult DM

Gunawardena H et al, Arthritis Rheum 2009
Espada et al, J Rheum 2009

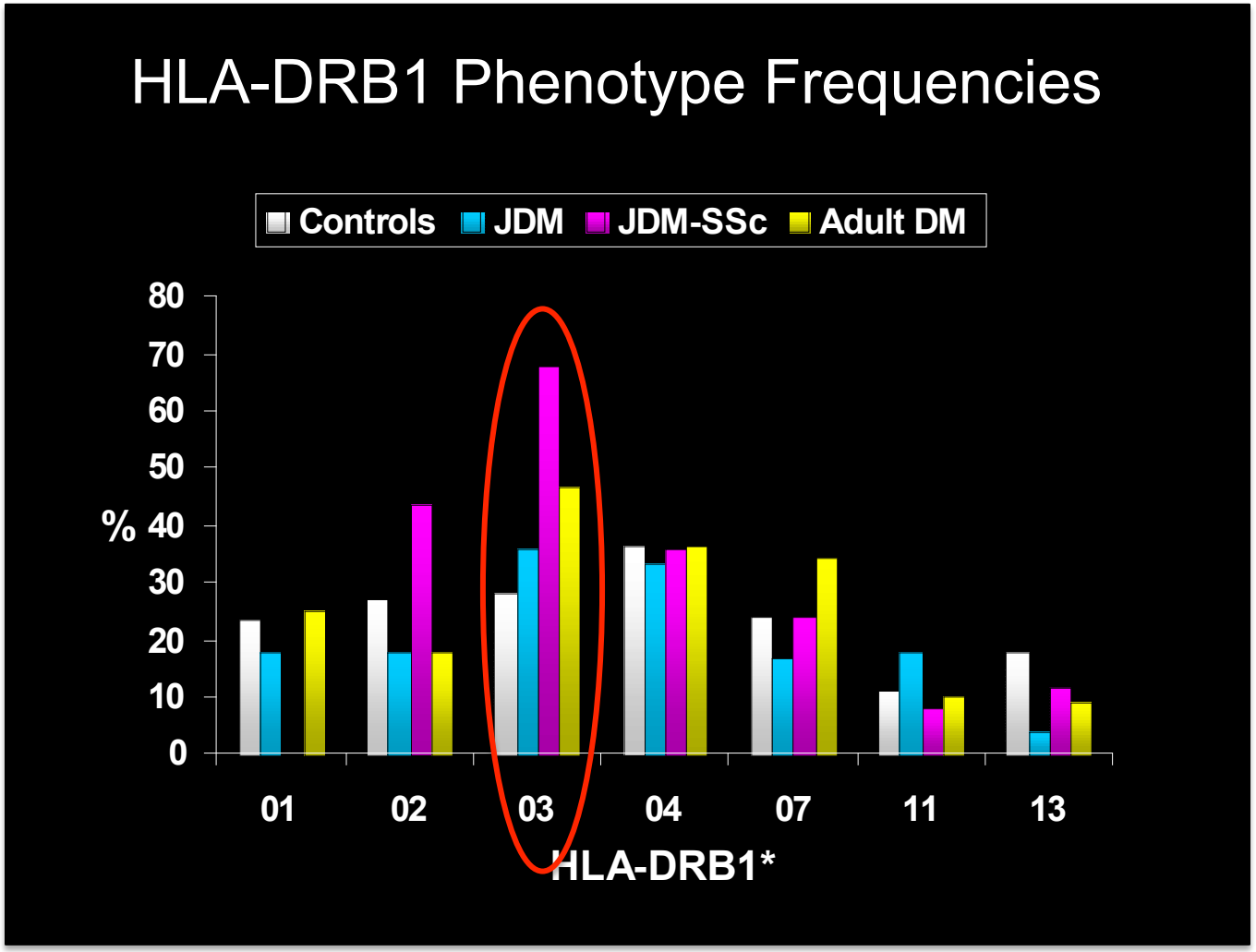
Autoantibodies and genetics in JDM

- HLA genetics
- Strong association between HLA and which auto antibodies are present



Wedderburn et al 2007

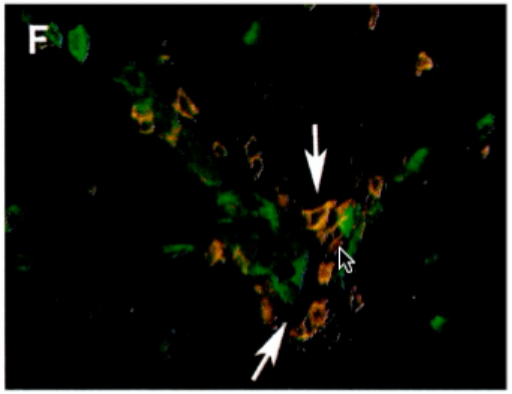
MHC (HLA) genetics JDM



Type 1 interferon in myositis

- Plasmacytoid DC CD123+CD4+CD11-

de Padilla et al A&R 2007

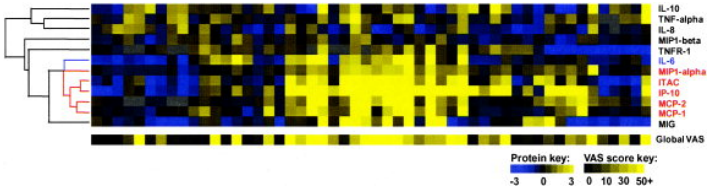


- TLR7, TLR 9 ligation leads to high IFN production

- Type 1 IFN signature correlates with disease activity MHC class I, MxA, IRF-7, MCP-1

Greenberg Neurology 2002, Tezak JI 2002

- Chemokines produced in response to IFN include MCP1, IP-10, ITAC – correlate with disease in JDM Biljic et al A & R 2009



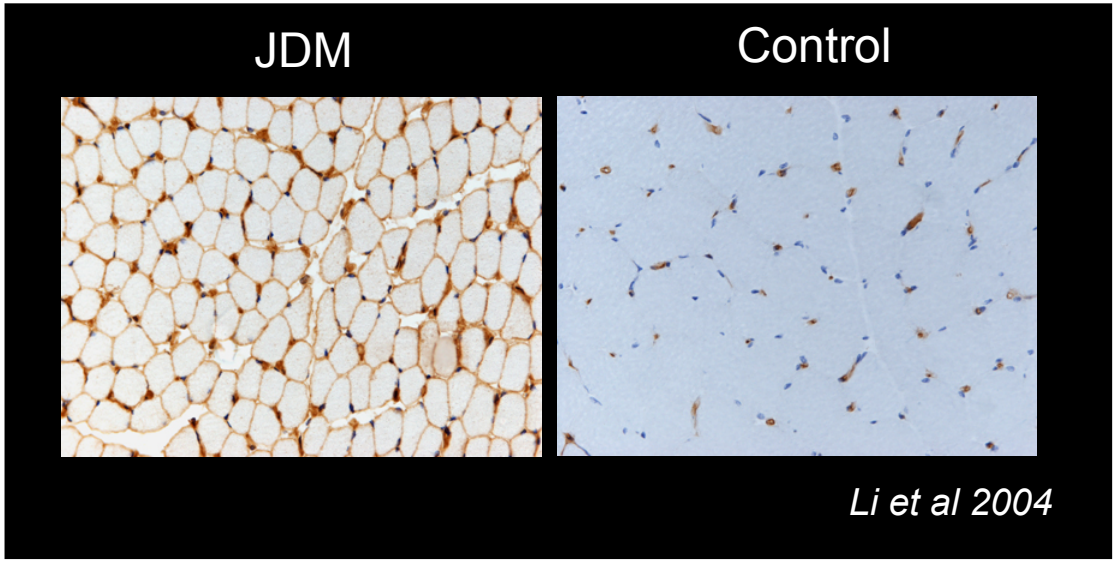
ER stress : role in myositis ?

Sensors for increased or misfolded proteins

Unfolded protein response (UPR) GRP78, GRP94, calreticulin : activation of PERK, IRE1 and ATF-6; alternate splicing of Xbp-1

Endoplasmic reticulum associated degradation (ERAD) Ubiquitination for degradation of excess protein in proteosome

Endoplasmic reticulum overload response (EOR) NFkB - cytokine production



Conclusions

- Modern management of JDM treat early and be aggressive
- Autoantibodies correlate with clinical phenotype
- Autoantibody production tightly linked to HLA types
- However key differences between children and adults
- Juvenile muscle more vulnerable to ER Stress and immune damage
- Recovery is more possible

gracias