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Epidemiology and Presentation of Inflammatory Myopathy

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Layout

- clinical features
- classification
- diagnostics
- risk factors

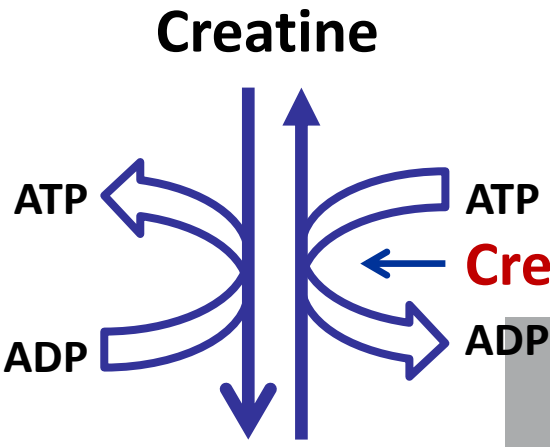
clinical features

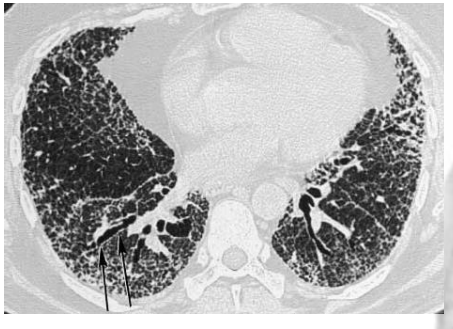
classification

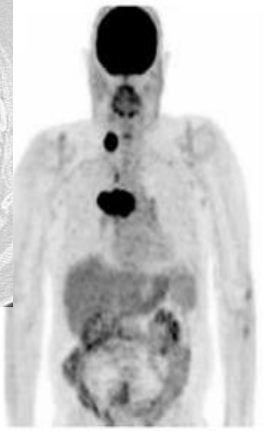
diagnostics

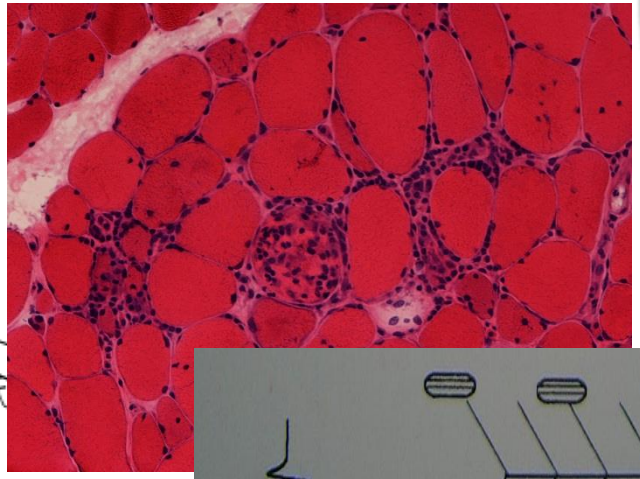
risk factors

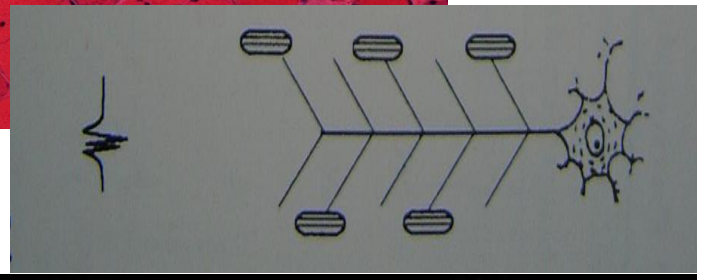
Myositis features

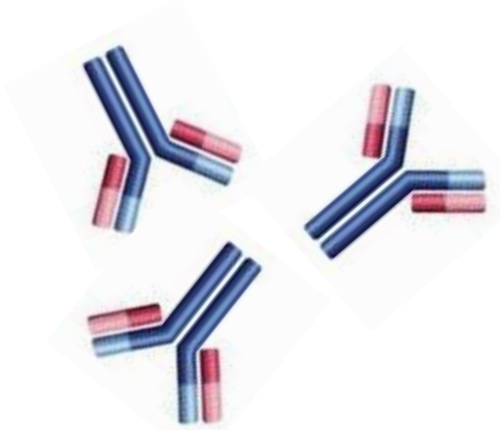


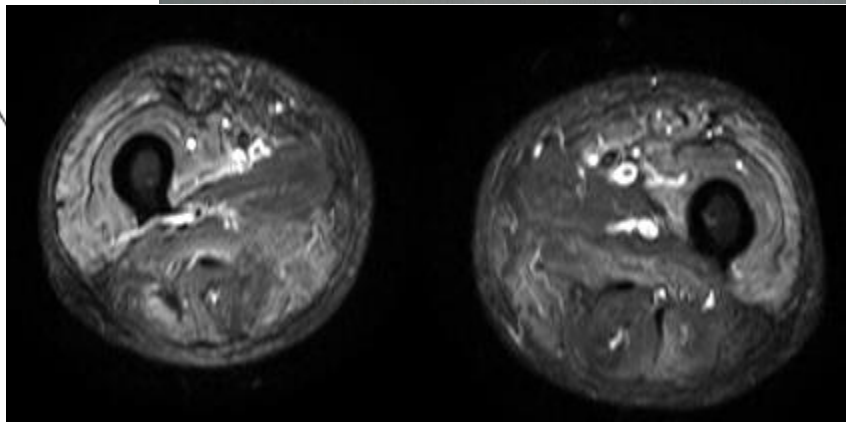


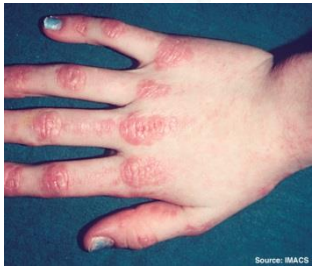


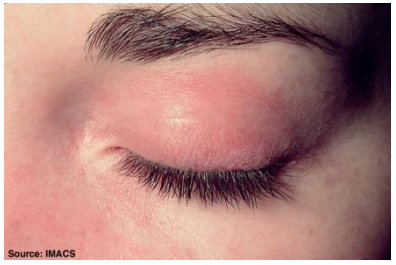












Epidemiology of Myositis / Idiopathic Inflammatory Myopathy

Annual incidence
5-10/million

Prevalence
~50-90/million

2 peaks of onset

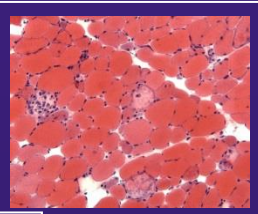
- Childhood (5-15 years)
- Midlife (30-50 years)

Females preferentially affected (~3:1)

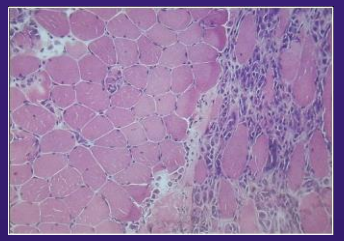
Mastaglia FL, Phillips BA, Rheum Dis Clin North Am 2002

Idiopathic Inflammatory Myopathy

Necrotizing Myopathy



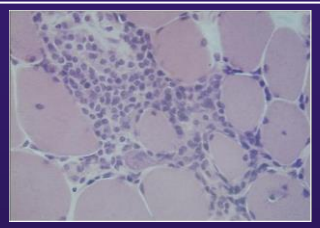
Dermatomyositis

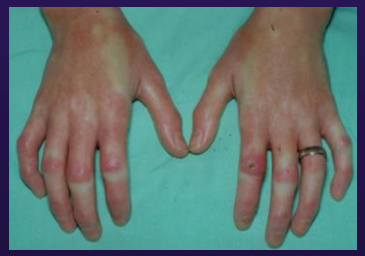


Malignancy

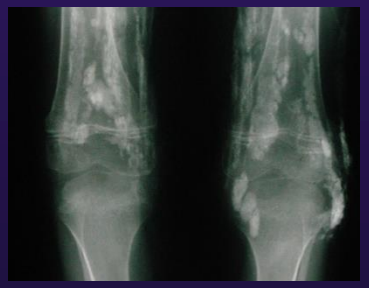
Polymyositis

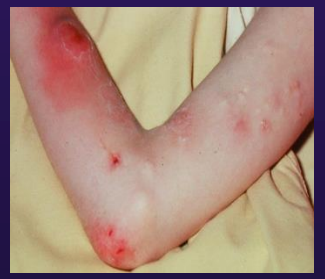
Inclusion Body Myositis





Myositis-CTD overlap





Juvenile dermatomyositis

Idiopathic inflammatory myopathy – what is it? (1)

Heterogeneous group of rare autoimmune diseases

Aetiology involves interactions between environmental and genetic risk factors

May also manifest in association with other connective tissue disorders

Extramuscular features can also occur

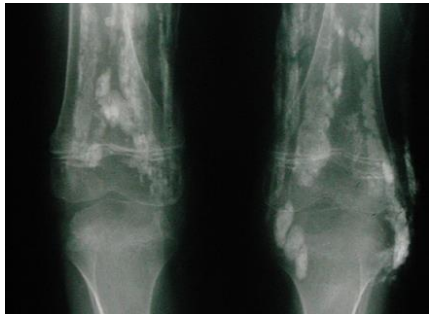
Idiopathic inflammatory myopathy – what is it? (2)

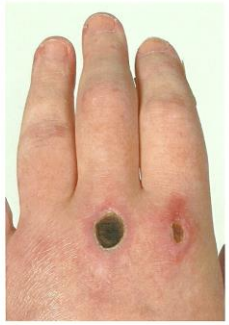
- Proximal weakness
- Rash (dermatomyositis)
- Myositis-specific/myositis-associated autoantibodies
- Raised muscle enzymes
- Inflammatory cell infiltrates in muscle tissue (myositis)
- Electrophysiological abnormalities

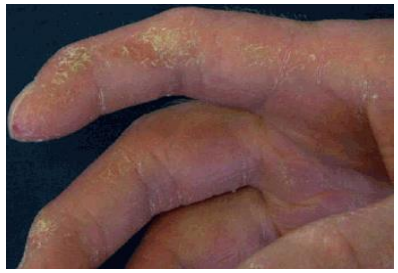
How do patients' present with IIM to rheum/neuro?

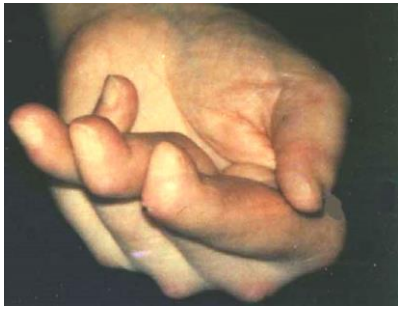
- Insidious onset of proximal weakness
- Myalgia
- Fatigue
- Dysphagia
- Dyspnoea
- Weight loss
- Skin abnormalities (including ulceration)
- Raynaud's
- Dry, cracked hands
- Arthralgia/arthritis

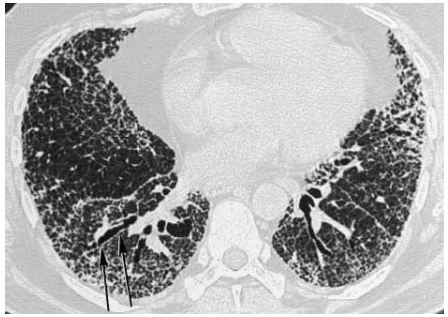
Extra-muscular features

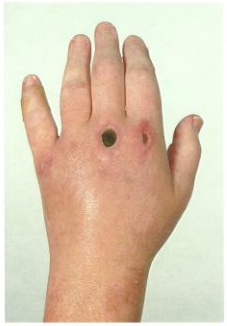


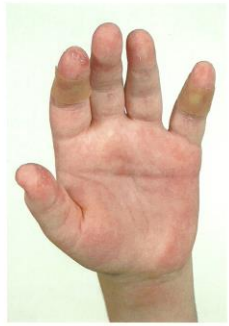


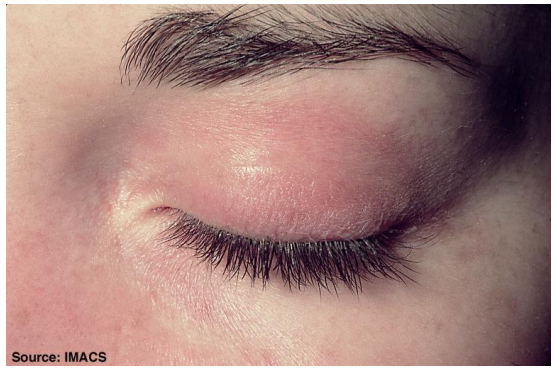


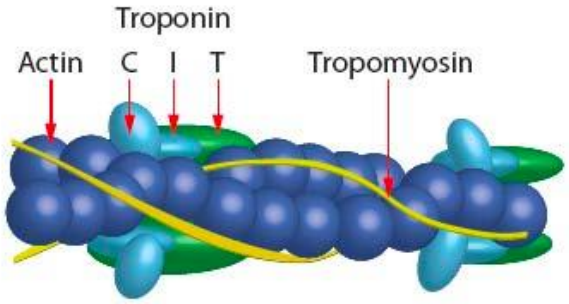












Slides courtesy of IMACS, Prof Oddis & McHugh

http://www.cytoskeleton.com/tropomyosin-troponin-complex-cs-tt05

Don’t forget that Arthritis can be a presenting feature of Idiopathic Inflammatory Myopathy

Table 2. Arthritis in myositis subtypes. Data are n (%).

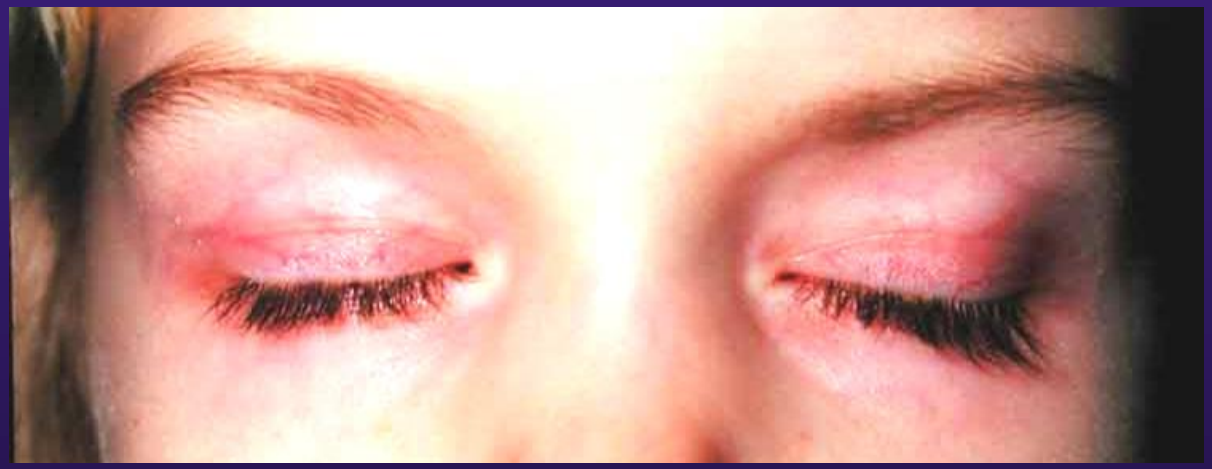
Diagnosis	Arthritis at Any Time*	Arthritis at Disease Onset**	Current Arthritis# (≥ 1 swollen joint)
PM (46)	27 (59)	19 (41)	17 (40)
DM (40)	22 (55)	15 (38)	11 (28)
CAM (8)	2 (25)	1 (13)	0 (0)
IMNM (11)	4 (36)	1 (13)	2 (18)
IBM (1)	1 (100)	1 (100)	1 (100)
Total (106)	56 (53)	39 (37)	31 (29)

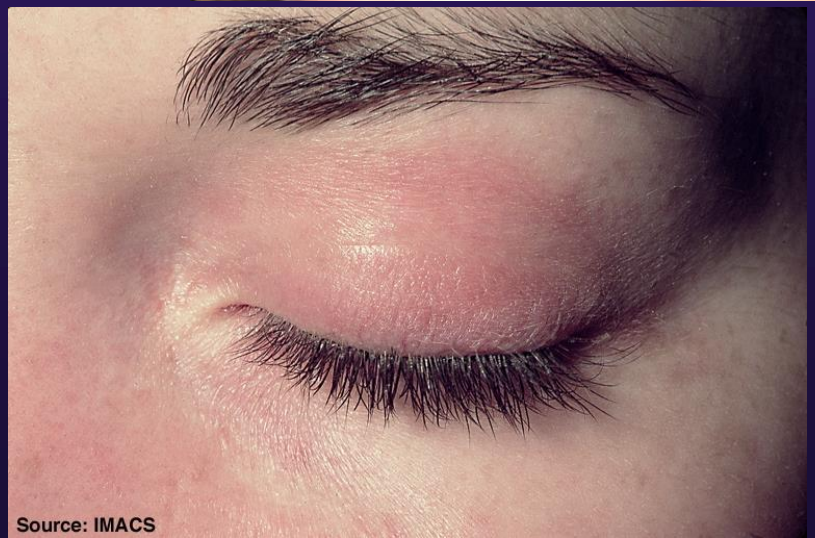
- 39/106 (37%) arthritis at presentation
- 23/106 (22%) arthritis preceded weakness
- 27/29 Jo-1 had arthritis at anytime

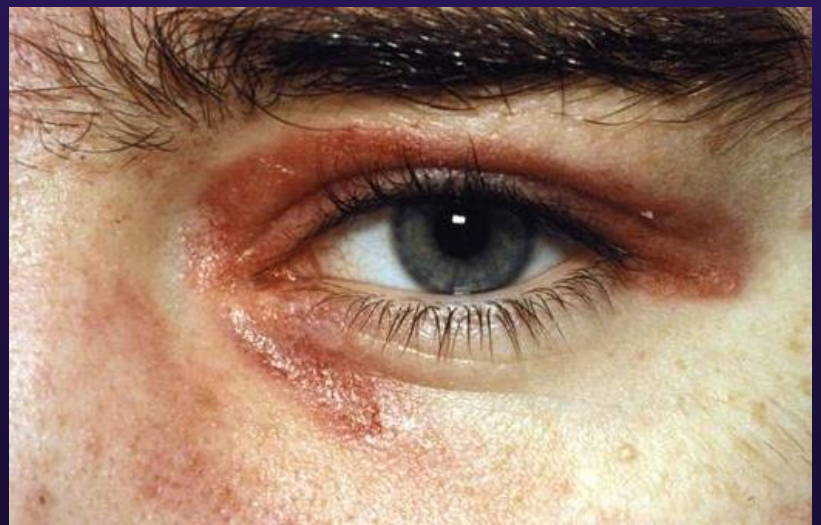
Klein et al. J Rheumatol. 2014 Jun;41(6):1133-9. doi: 10.3899/jrheum.131223. Epub 2014 May 1.

Heliotrope rash

- Violaceous to erythematous discrete or confluent macules confined to the upper eyelids.

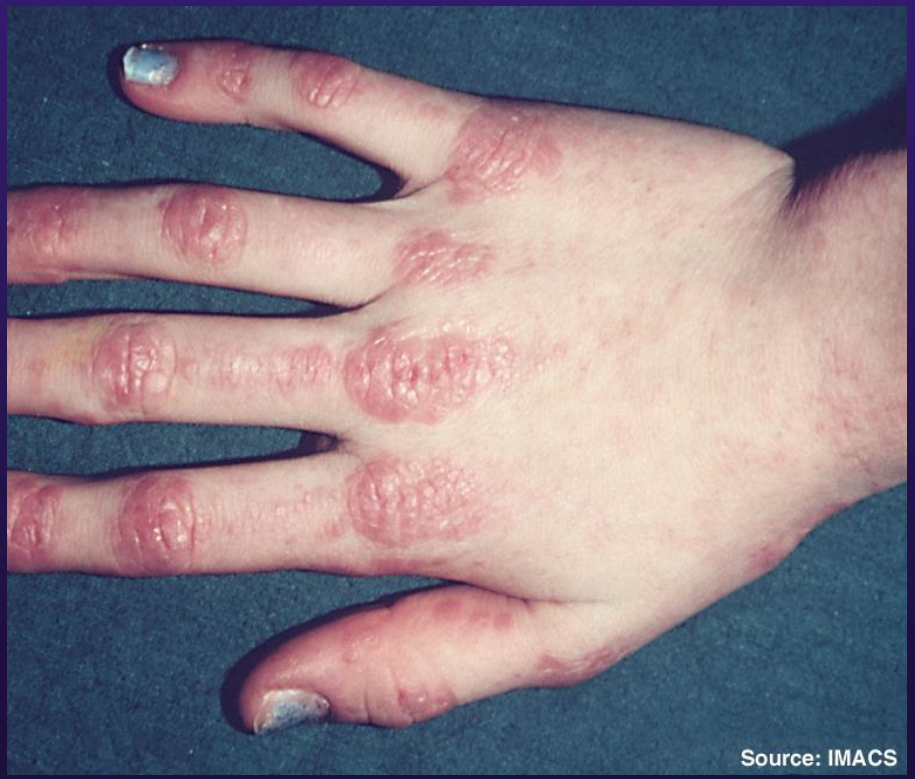


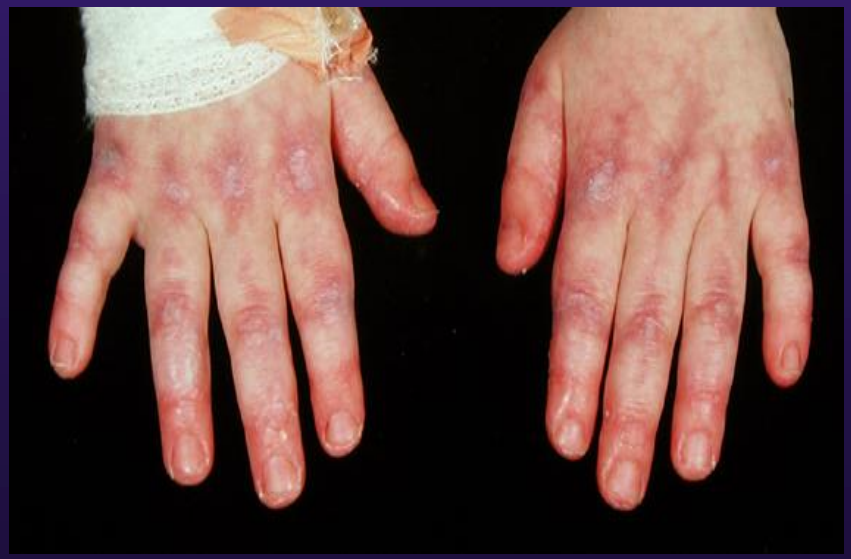




Gottron's papules

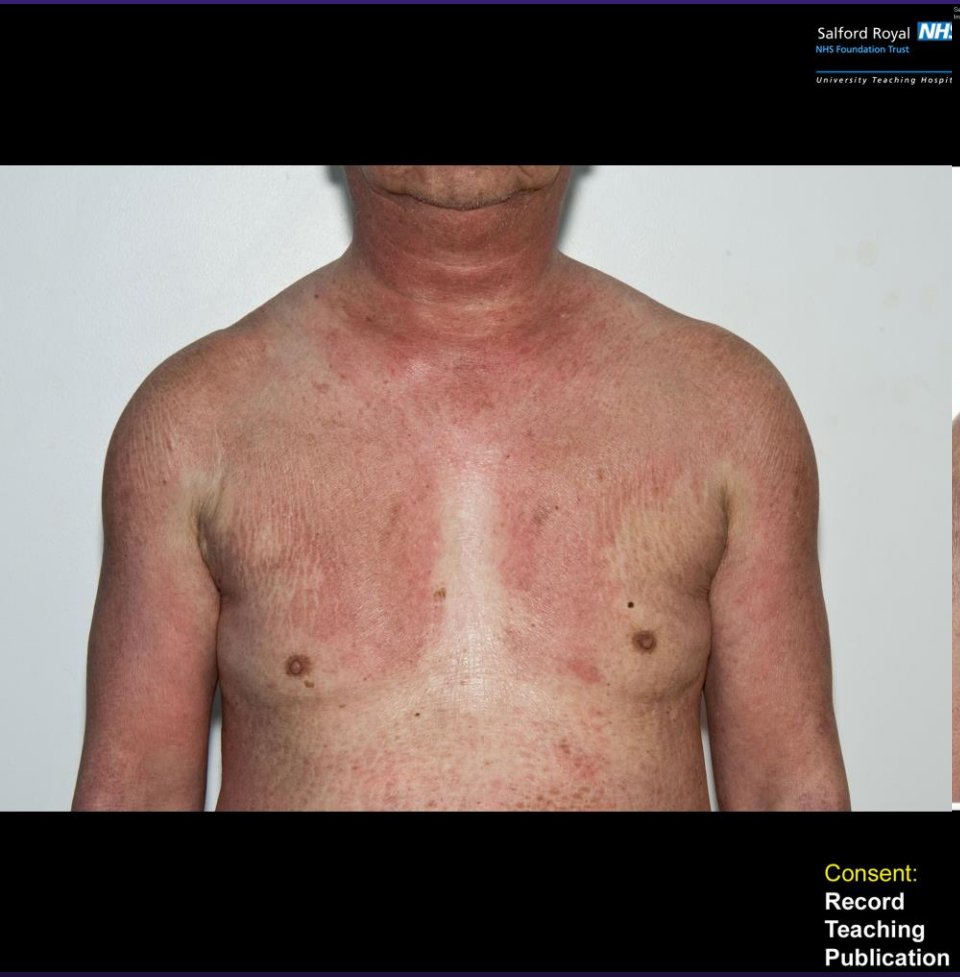
- Erythematous to violaceous papules and plaques over the extensor surfaces of MCP and IP joints & other large joints in a symmetric distribution.



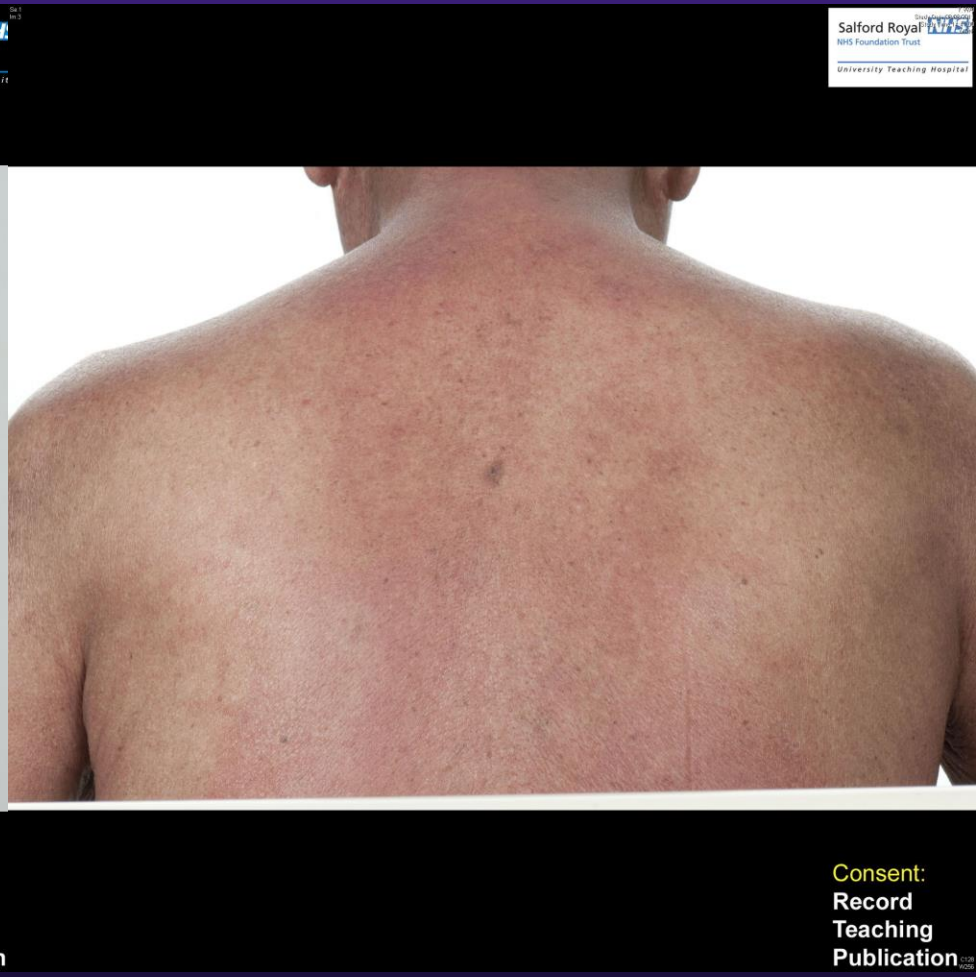


•Discrete and confluent macular erythema over the lower anterior neck and upper anterior chest

•Discrete and confluent macular erythema in a shawl distribution

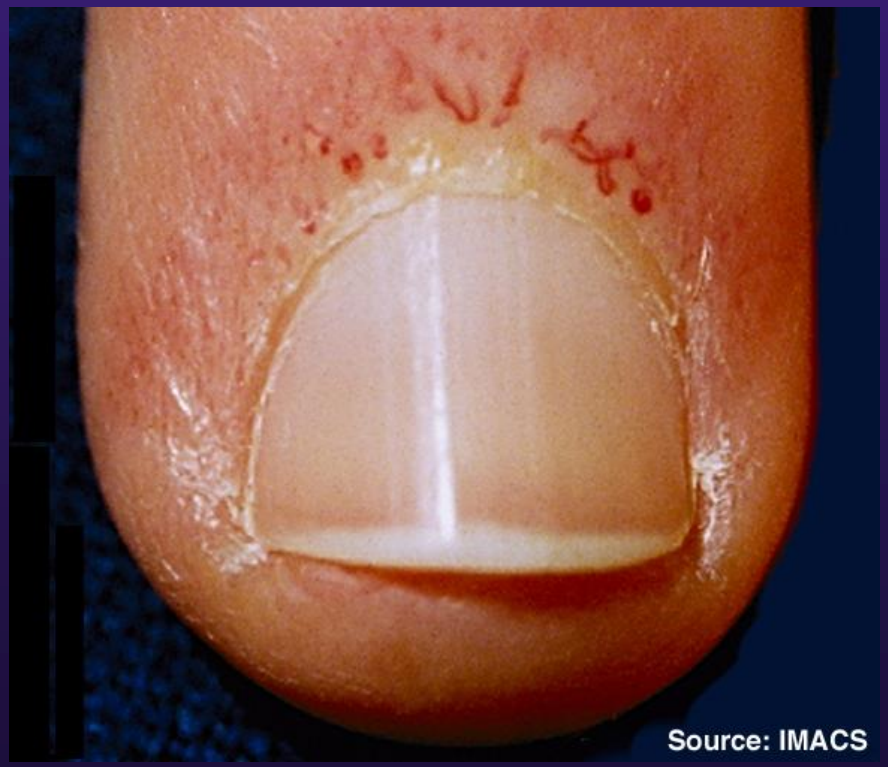


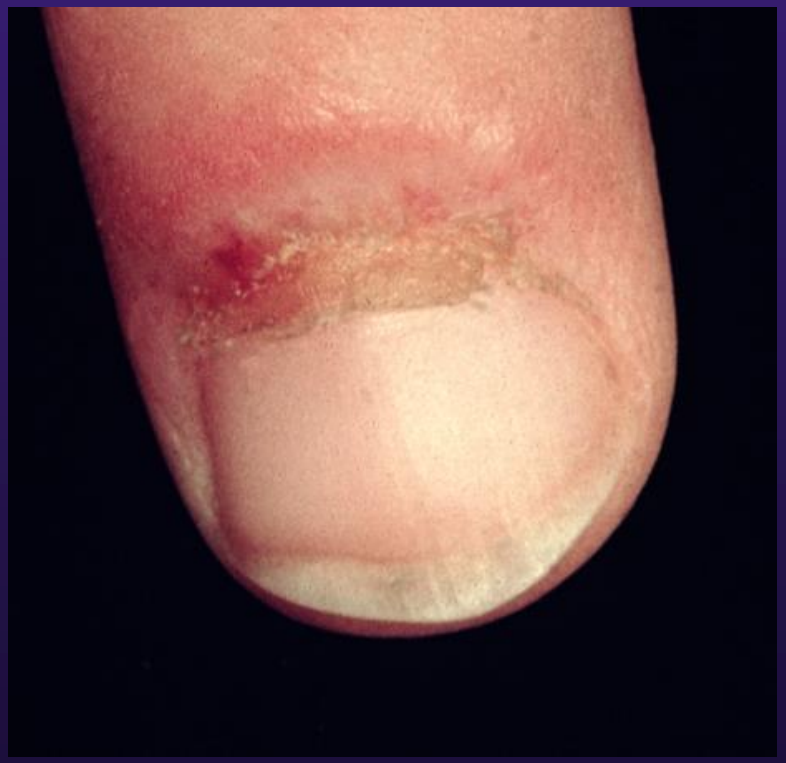
V SIGN



SHAWL SIGN

Nail changes





clinical features

classification

diagnostics

risk factors

Bohan and Peter diagnostic criteria for polymyositis / dermatomyositis

1	Symmetrical weakness of limb-girdle muscles and anterior neck flexors		
2	Muscle biopsy evidence typical of myositis		
3	Elevation of serum skeletal muscle enzymes, particularly CK		
4	Typical EMG features of myositis		
5	Typical DM rash, including heliotrope and Gottron's papules		
For the diagnosis of PM:		For the diagnosis of DM:	
Definite:	All of items 1-4	Definite:	Item 5 plus 3 of items 1-4
Probable:	3 of items 1-4	Probable:	Item 5 plus 2 of items 1-4
Possible:	2 of items 1-4	Possible:	Item 5 plus 1 of items 1-4

Exclusion criteria: congenital muscular dystrophies, central or peripheral neurological disease, infectious myositis, metabolic/endocrine myopathies and myasthenia gravis.

Bohan A, Peter JB, N Eng J Med 1975

New classification criteria for myositis

VARIABLE	SCORE POINTS	
	Without muscle biopsy data	With muscle biopsy data
18 ≤ Age of onset of first symptom < 40	1.3	1.5
Age of onset of first symptom ≥ 40	2.1	2.2
Clinical Muscle Variables		
Objective symmetric weakness, usually progressive, of the proximal upper extremities	0.7	0.7
Objective symmetric weakness, usually progressive, of the proximal lower extremities	0.8	0.5
Neck flexors are relatively weaker than neck extensors	1.9	1.6
In the legs proximal muscles are relatively weaker than distal muscles	0.9	1.2
Skin variables		
Heliotrope rash	3.1	3.2
Gottron´s papules	2.1	2.7
Gottron's sign	3.3	3.7
Other Clinical Variables		
Dysphagia or esophageal dysmotility	0.7	0.6
Laboratory Variables		
Elevated serum levels of creatine kinase (CK) *or*, Serum lactate dehydrogenase (LDH) *or*, Serum aspartate aminotransferase (ASAT) *or*, Serum alanine aminotransferase (ALAT)	1.3	1.4
Anti-Jo-1 (anti-Histidyl-tRNA synthetase) autoantibody positivity	3.9	3.8
Muscle Biopsy Variables		
Endomysial infiltration of mononuclear cells surrounding, but not invading, myofibers		1.7
Perimysial and/or perivascular infiltration of mononuclear cells		1.2
Perifascicular atrophy		1.9
Rimmed vacuoles		3.1

Tjarnlund et al, Ann Rheum Dis 2013: vol 72, suppl 3, p60

http://www.imm.ki.se/biostatistics/calculators/iim/

Performance of new criteria

PERFORMANCE OF NEW AND EXISITING CLASSIFICATION / DIAGNOSTIC CRITERIA FOR IIM							
Performance (%)	**New classification criteria[a]**		**Bohan & Peter[b]**	**Tanimoto *et al.***	**Targoff *et al.*[b]**	**Dalakas & Hohlfeld[b]**	**Hoogendijk *et al.*[b]**
	Without muscle biopsy data	With muscle biopsy data					
Sensitivity	86	90	98	96	93	6	52
Specificity	84	90	55	31	89	99	97
Correctly classified	85	90	86	79	91	45	70
Correct classification per subgroup (%)							
Amyopathic DM	100	100	25	14	0	0	0
DM	98	100	100	96	99	7	83
Hypomyopathic DM	100	100	80	40	67	0	20
IMNM	100	100	100	100	100	0	10
IBM	68	94	97	97	91	1	1
JDM	98	96	100	96	98	5	86
PM	83	90	95	100	85	11	9
Non IIM	9	11	45	69	11	1	3

[a]Cut point for probability: 55%

[b]Definite and probable PM and DM

Many causes of raised CK!

1. Muscle trauma	a) Muscle injury / Needle stick b) EMG c) Surgery d) Convulsions, delirium tremens	
2. Diseases affecting muscle	a) Myocardial infarction b) Rhabdomyolysis g) Infectious myositis c) Metabolic myopathies d) Carnitine palmityltransferase II deficiency e) Mitochondrial myopathies	f) Dystrophinopathies h) Amyotrophic lateral sclerosis i) Neuromyotonias h) Idiopathic inflammatory myopathy
3. Drug/toxin-induced myopathy	a) Lipid-lowering agents, especially statins b) Alcoholic myopathy c) Drugs of abuse: e.g. cocaine, amphetamines, phencyclidine d) Malignant hyperthermia / neuroleptic malignant syndrome e) Other meds: e.g. zidovudine, colchicine, chloroquine, ipecac	
4. Drug-induced CK elevation	Inhibition of excretion: e.g. barbiturates, morphine, diazepam	
5. Endocrine and metabolic abnormalities	a) Hypothyroidism b) Hypokalemia c) Hyperosmolar state or ketoacidosis d) Diabetic nephrotic syndrome with oedema e) Renal failure	
6. Elevation without disease	a) Strenuous, prolonged, and/or unaccustomed exercise b) Ethnic group (black > white) c) Increased muscle mass	

Targoff IN.

Rheum Dis Clin North Am 2002;28:859–890

Differential diagnosis of muscle weakness

Inherited myopathies	Muscular dystrophies: Duchenne's, fascioscapulohumeral, limb girdle, Becker's, Emery Dreifuss, distal, ocular Congenital myopathies: nemaline, mitochondrial, centronuclear, central core
Neurologic	Denervating conditions: spinal muscular atrophies, amyotrophic lateral sclerosis Neuromuscular junction disorders: Eaton-Lambert syndrome, myasthenia gravis Myotonic disease: dystrophia myotonica, myotonia congenita, PROMM Other: Guillain-Barre syndrome, chronic autoimmune polyneuropathy
Metabolic	Glycogen storage diseases: acid maltase deficiency, McArdle's, PFK Lipid storage myopathies: carnitine palmityltransferase II deficiency Nutritional: vitamin E deficiency, malabsorption Other: uraemia, hepatic failure, alcoholism, acute intermittent porphyria, diabetic plexopathy
Endocrine myopathies	Hyper/hypothyroidism, acromegaly, Cushing's syndrome, Addison's disease, vitamin D deficiency, hyper/hypocalcaemia, hypokalaemia
Drug induced myopathies	Statins, D-penicillamine, clofibrate, chloroquine, amiodarone, vincristine, zidovudine
Infections	Acute viral: influenza, hep B, echovirus, rickettsia, coxsackie, rubella, vaccine-associated Bacterial pyomyositis: *staphylococcus, streptococcus, clostridium perfringens*, leprosy Parasites: *toxoplasma, trichinella, schistosoma, cysticercus*
Other connective tissues disorders	Rheumatoid arthritis, systemic sclerosis, systemic lupus erythematosus
Miscellaneous	Periodic paralyses, carcinomatous neuromyopathy, acute rhabdomyolysis, myositis ossificans, microembolisation by atheroma or carcinoma

Oddis CV, Rheum Dis Clin North Am 2002;28:979-1001

clinical features

classification

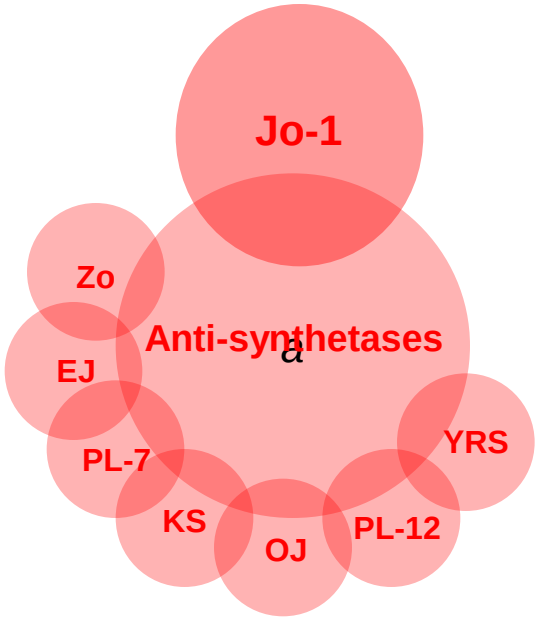
diagnostics

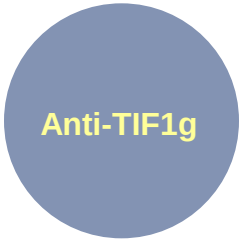
risk factors

Myositis-specific autoantibodies

Myositis specific autoantibodies ⟶ Clinical phenotypes in adults and children

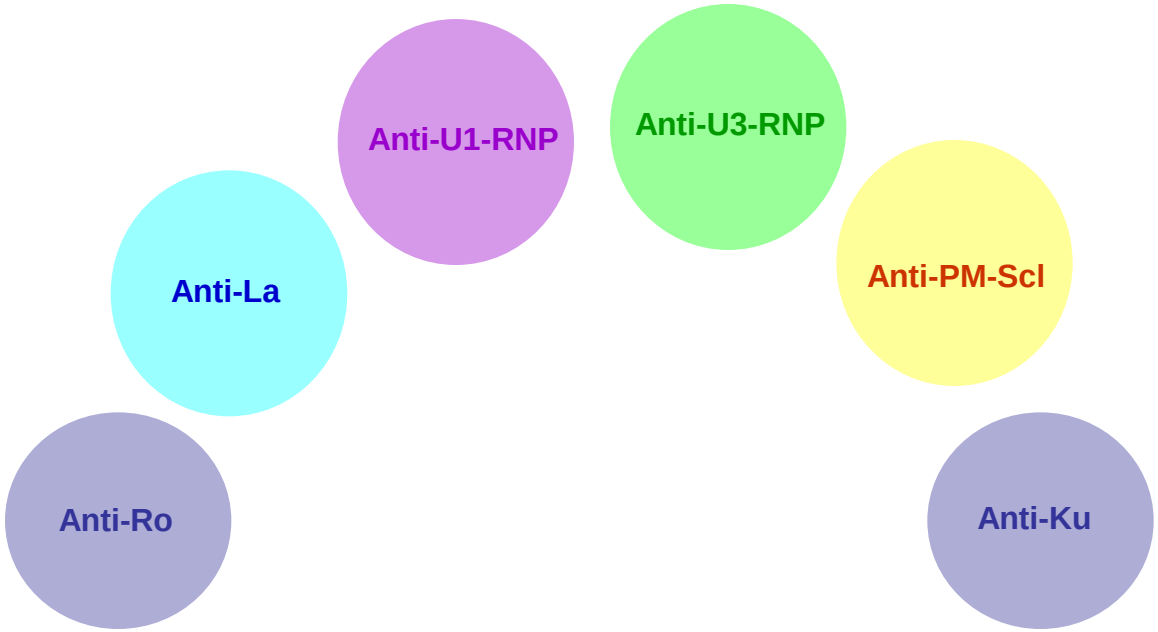
Anti-synthetase syndrome	Necrotizing myopathy	Amyopathic dermatomyositis	Dermatomyositis
Fever Raynauds Lung fibrosis Myositis Arthropathy Mechanics hands +/- rash	High CK	Rash *sine* myositis Hypomyopathic Rash precedes myositis	Rash Malignancy Calcinosis/vasculitis (children)





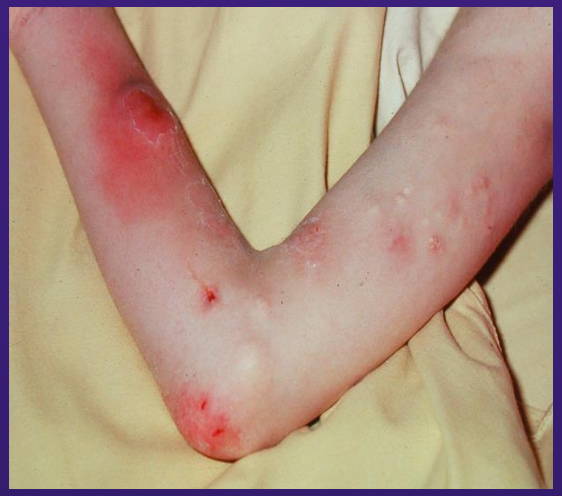
Slide adapted from Dr Gunawardena

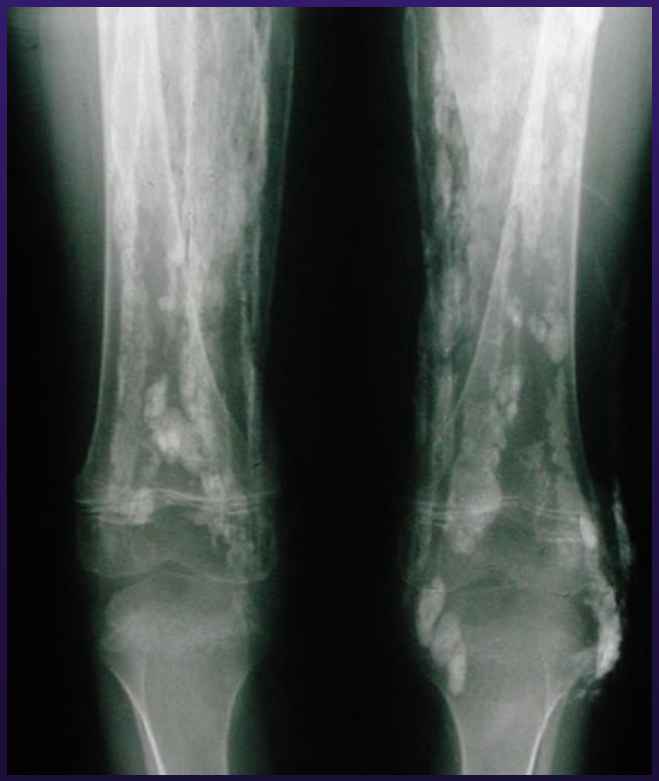
Myositis-associated antibodies



Overlap syndromes

- SLE
- SSc
- Sjogren's
- MCTD
- RA
- Anti-phospholipid



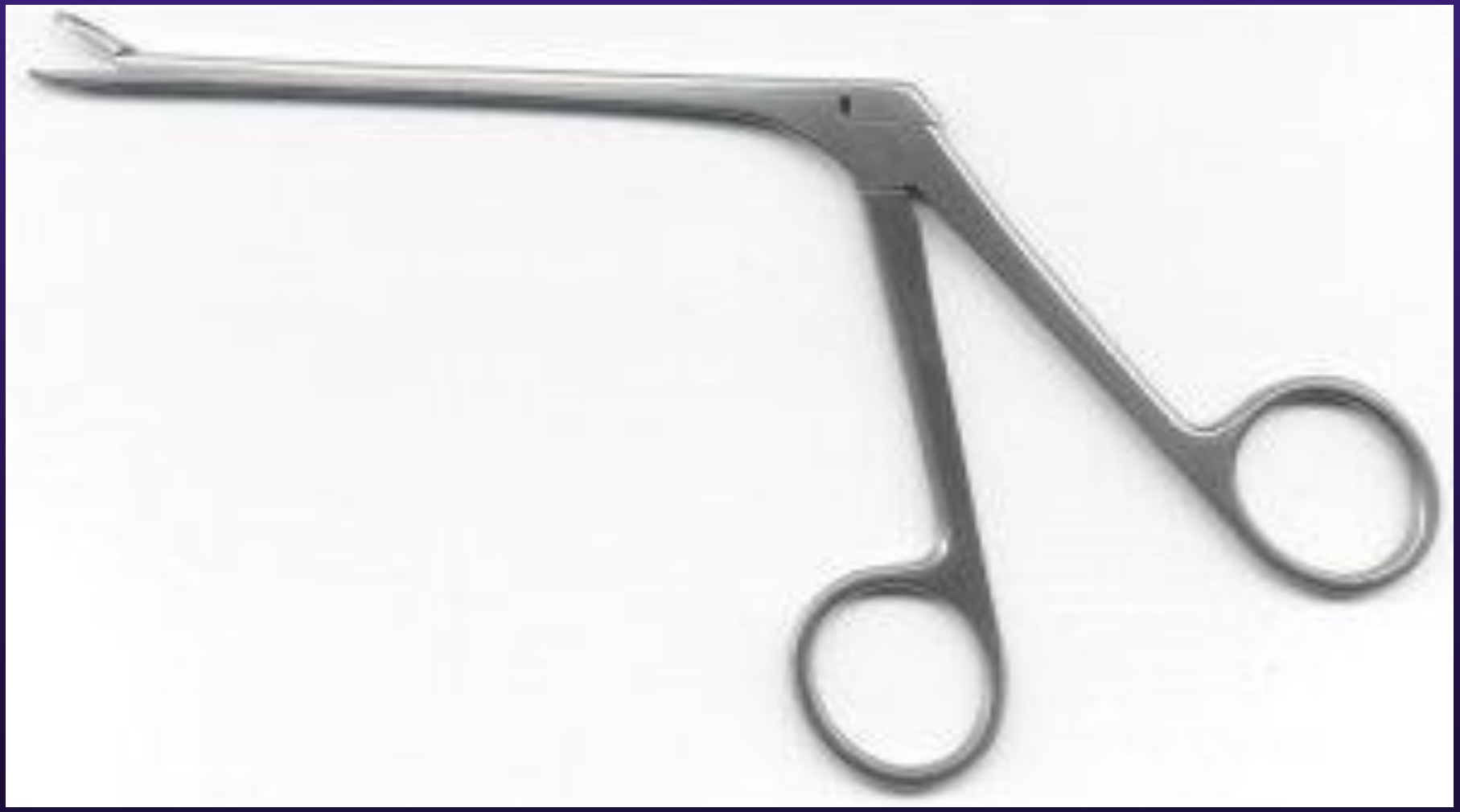


Juvenile dermatomyositis

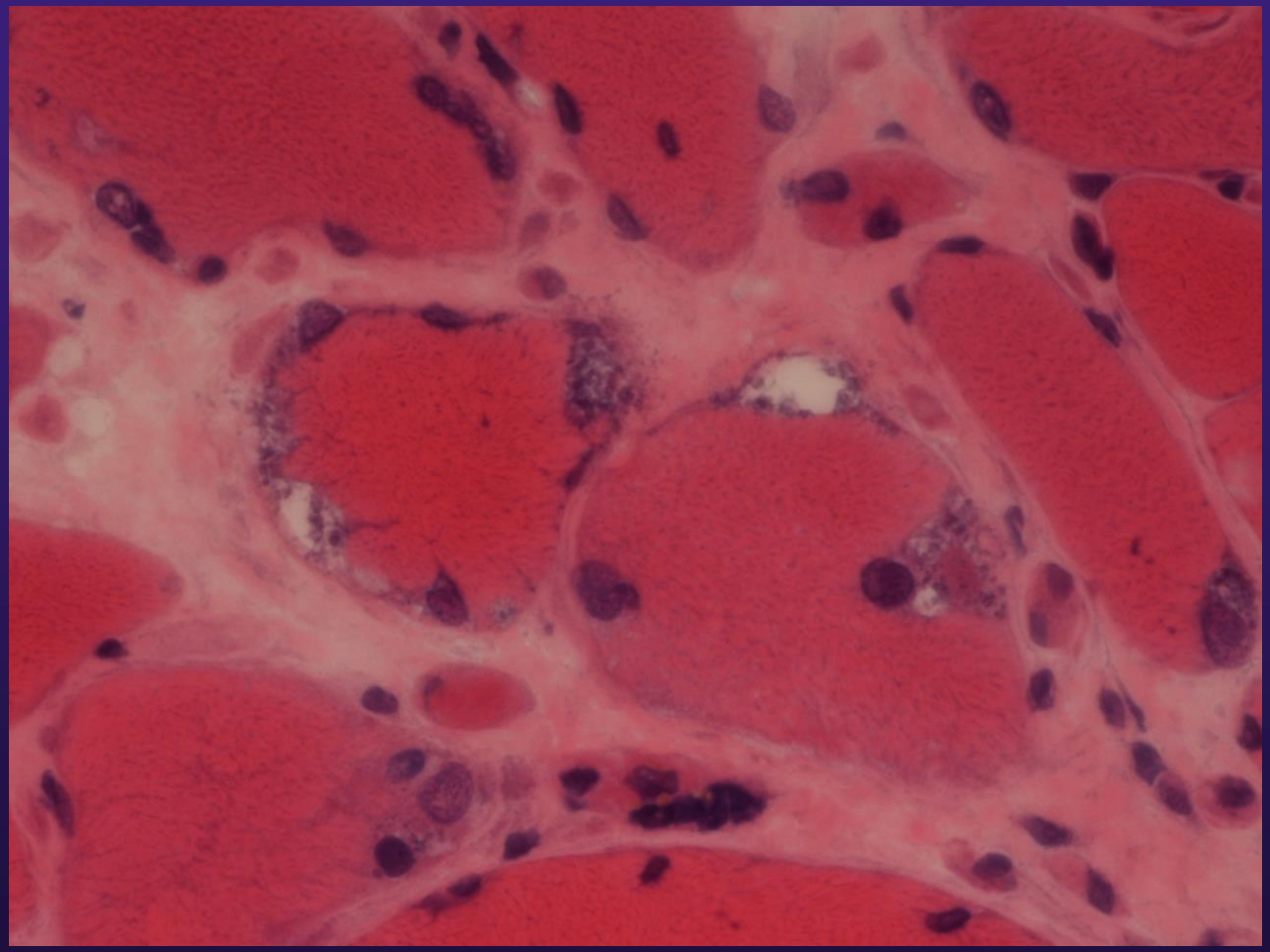
- 2 - 3 / 1,000,000 / year[1-3]
- Increased incidence with age
- Presenting symptoms
  - malaise, irritability
  - anorexia, weight loss
- Widespread vasculitis
- Calcinosis in late disease
- No link with malignancy

[1]Symmons et al, 1995; [2]Oddis et al, 1990; [3]Benbasset et al, 1980

Percutaneous Muscle Biopsy Forceps (Conchotome-type)



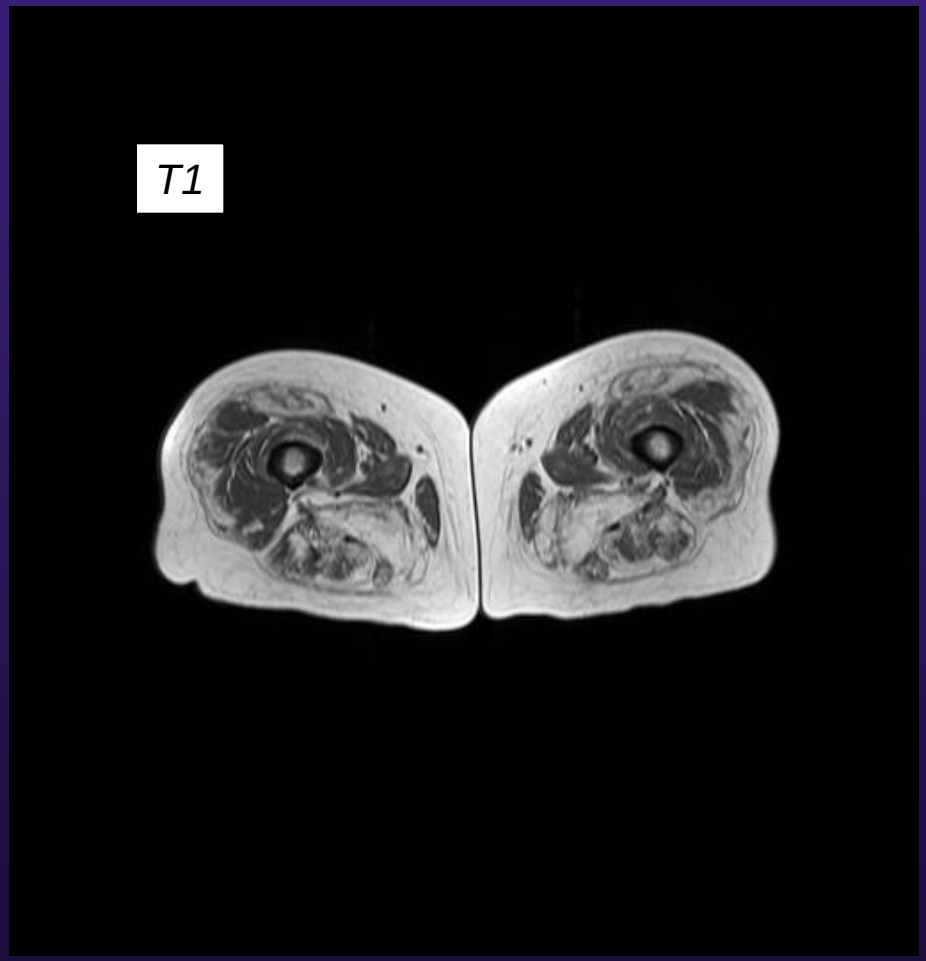
R tibialis anterior muscle biopsy

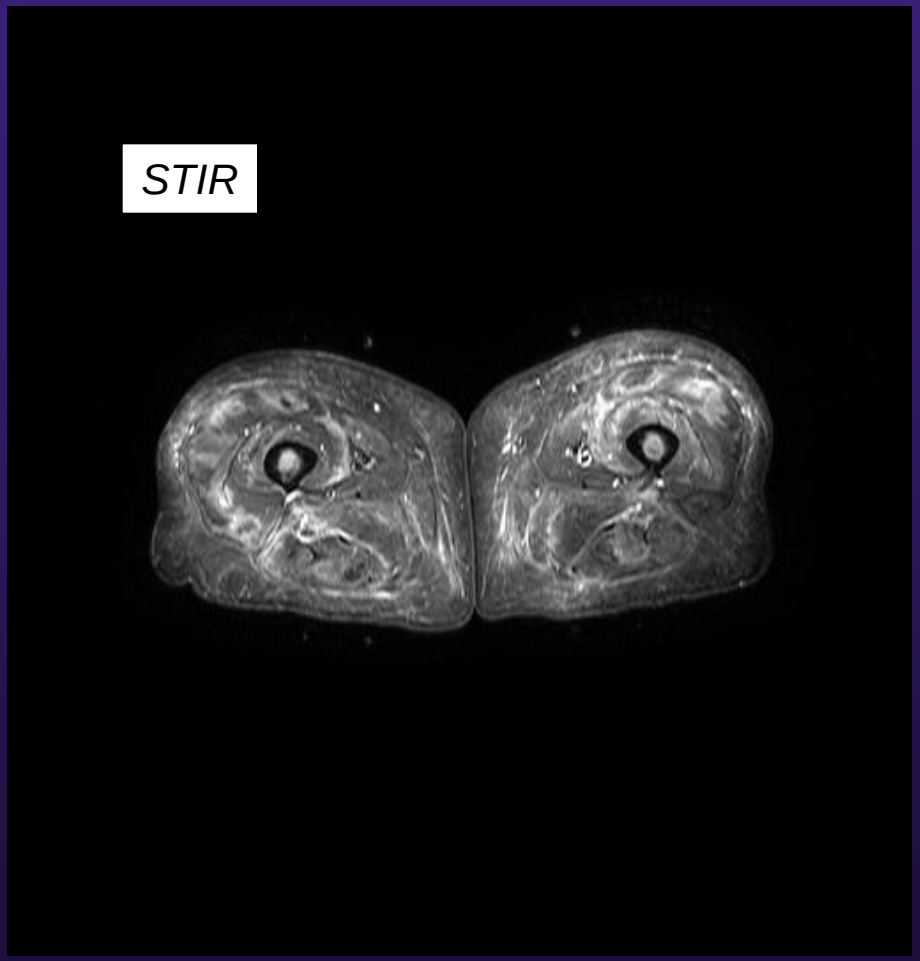


Recommended bloods, ideally 2 muscle enzymes

- CK
- LDH
- Aldolase
- Troponin
- Ferritin (ILD)
- Antibody screen
- ?Cancer markers

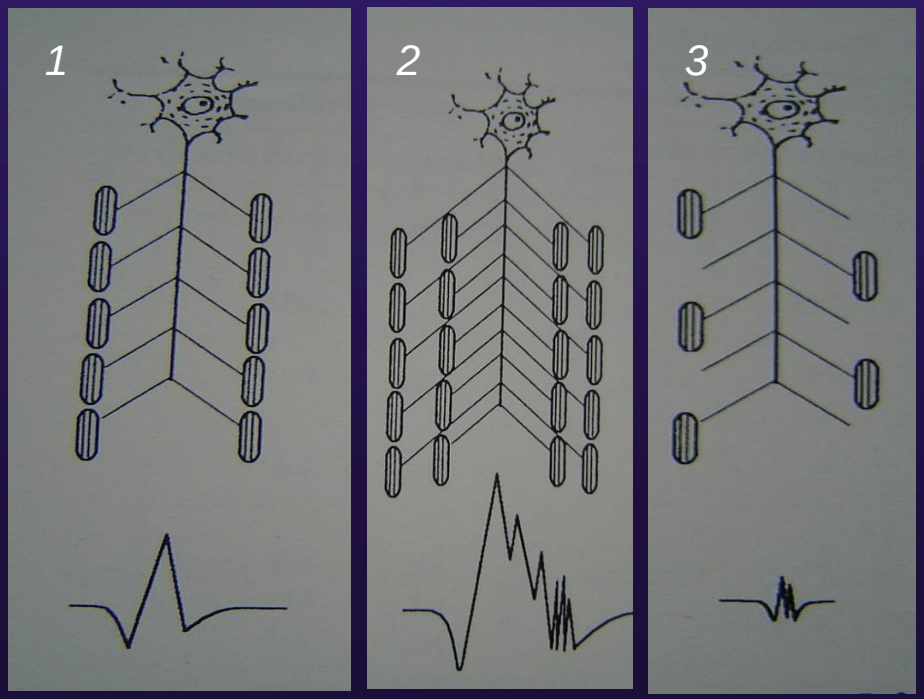
Use of muscle MR





EMG

- Acute - Spontaneous activity with fibrillation potentials (acute damage to motor end plates & terminal motor nerves)
- Chronic – Short-duration, low amplitude polyphasic MAPs (loss of muscle fibres)



1 Normal

2 Neurogenic

3 Myopathic

Images courtesy of Dr Marshall

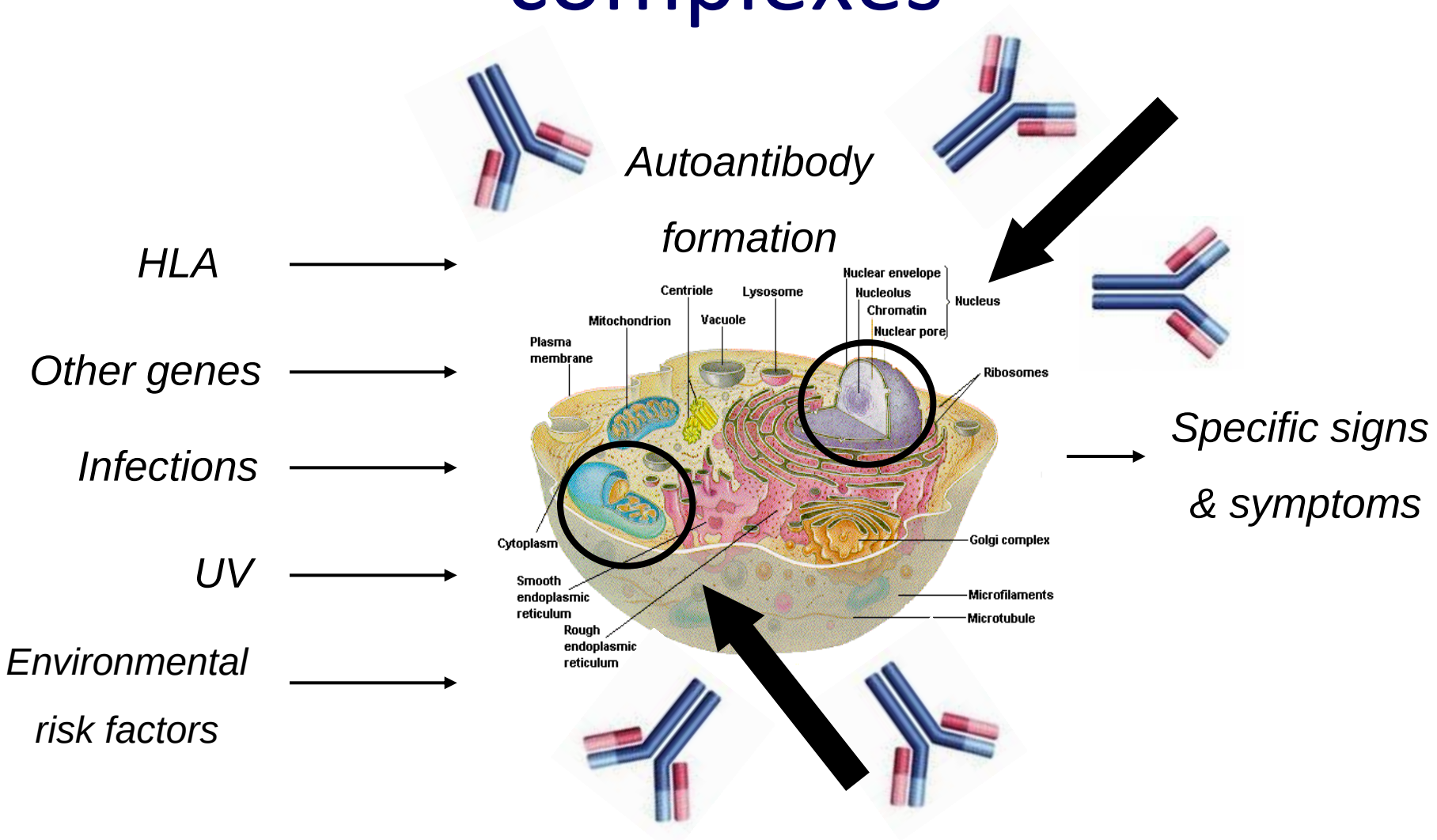
clinical features

classification

diagnostics

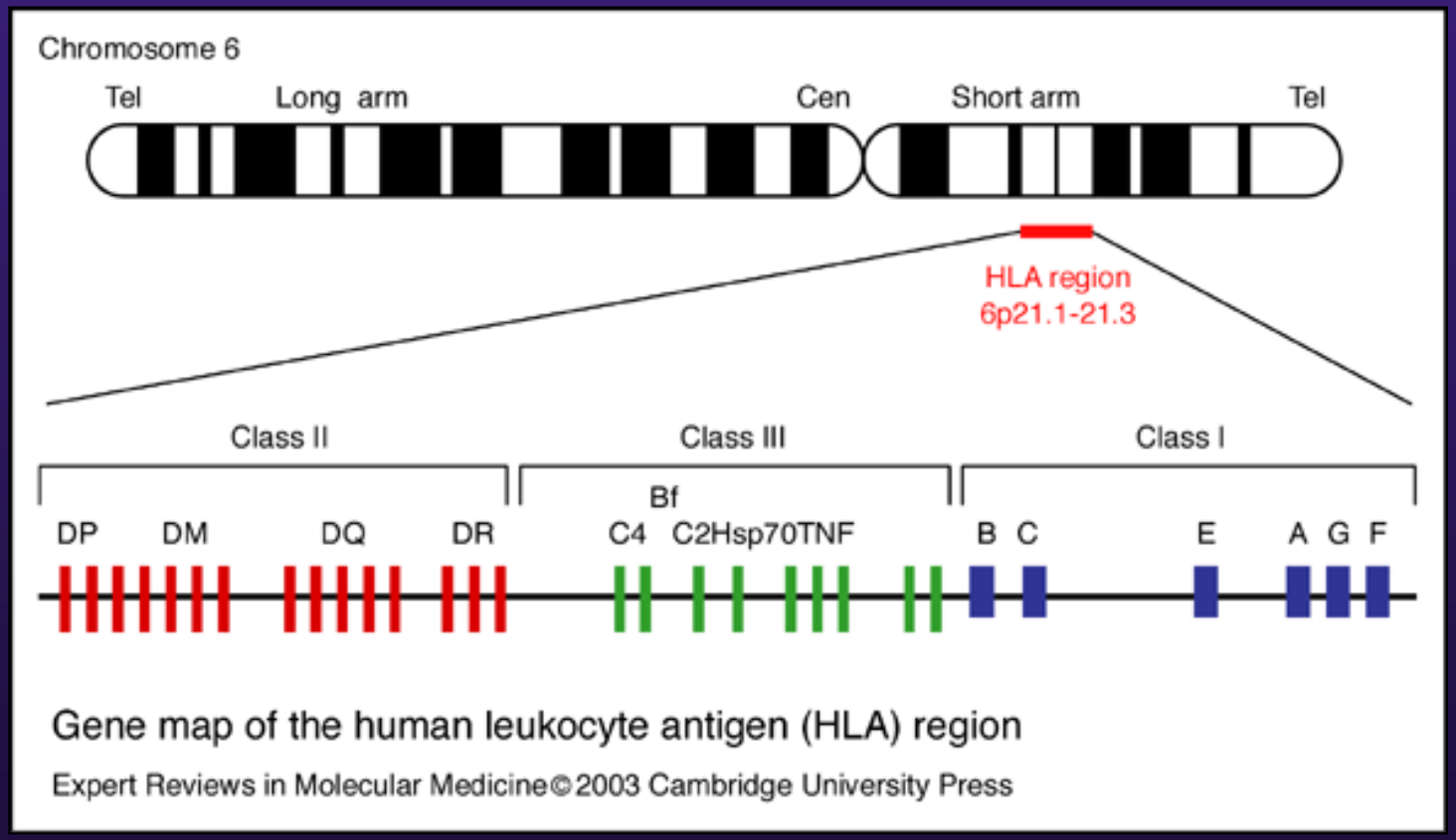
risk factors

Sign-symptom laboratory complexes



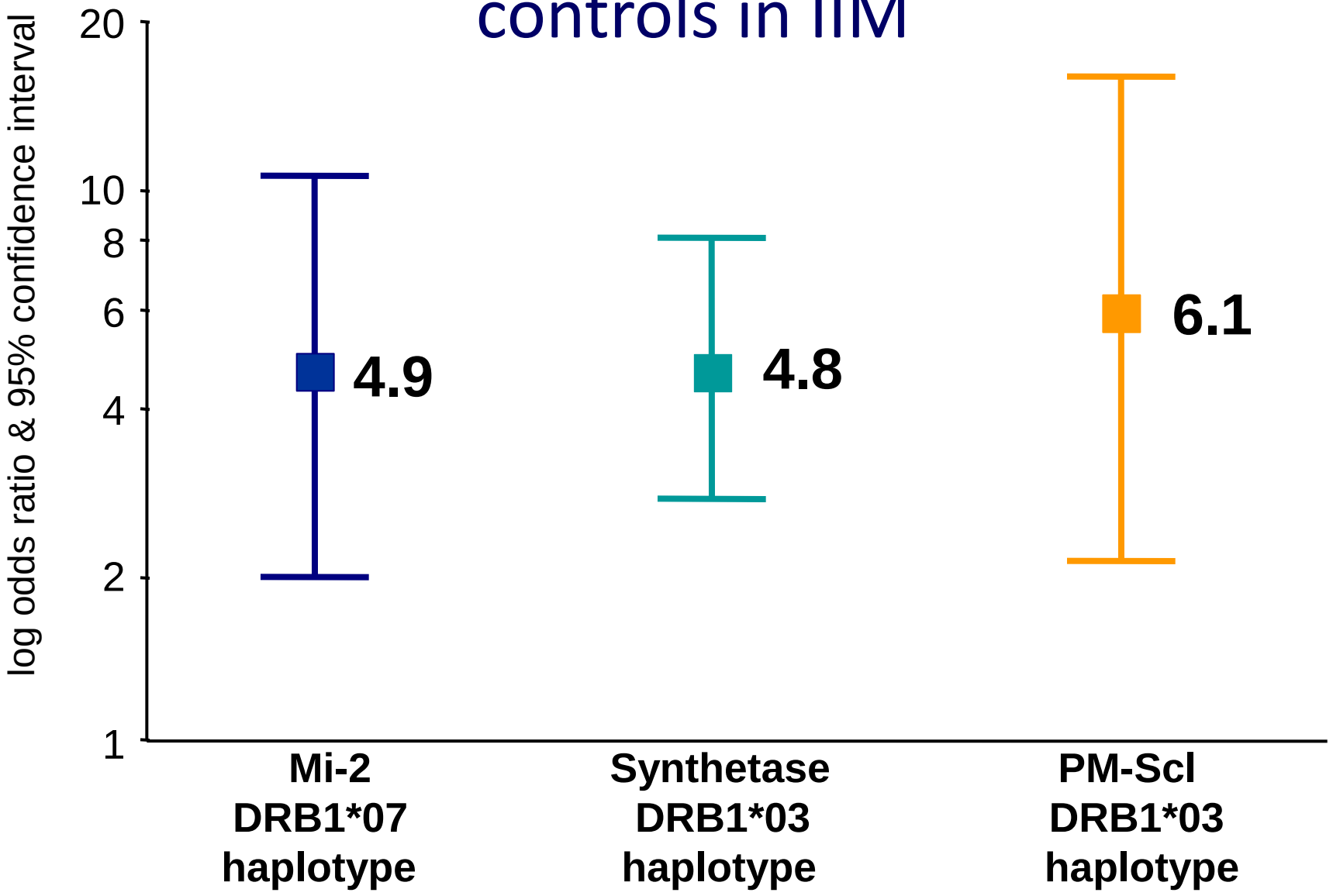
Hood E: Environ Health Perspect 2003, 111:A274–A276, picture courtesy of Dr Gunawardena.

HLA region



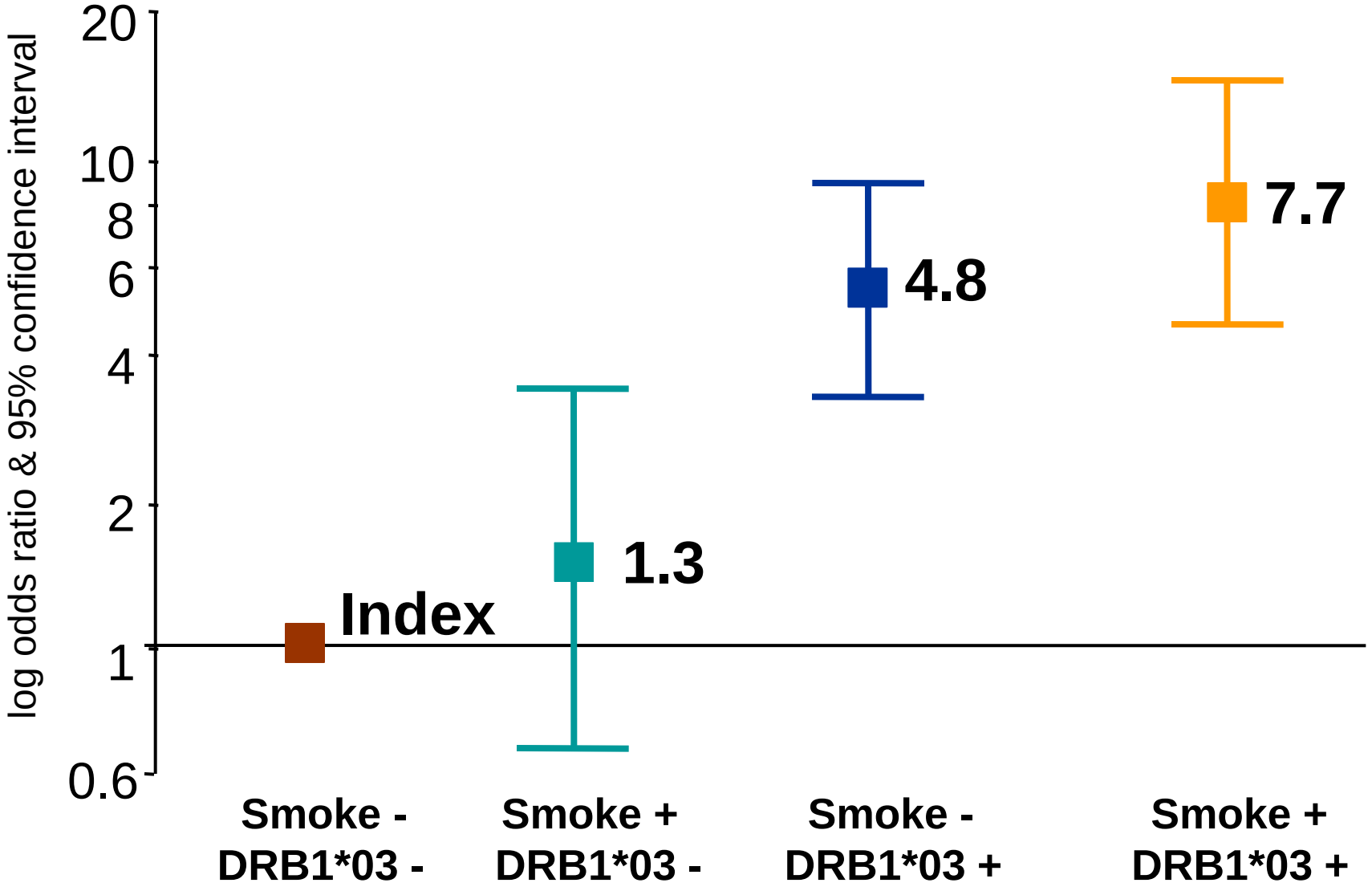
Gene map of the human leukocyte antigen (HLA) region

HLA haplotype-antibody associations *vs.* controls in IIM



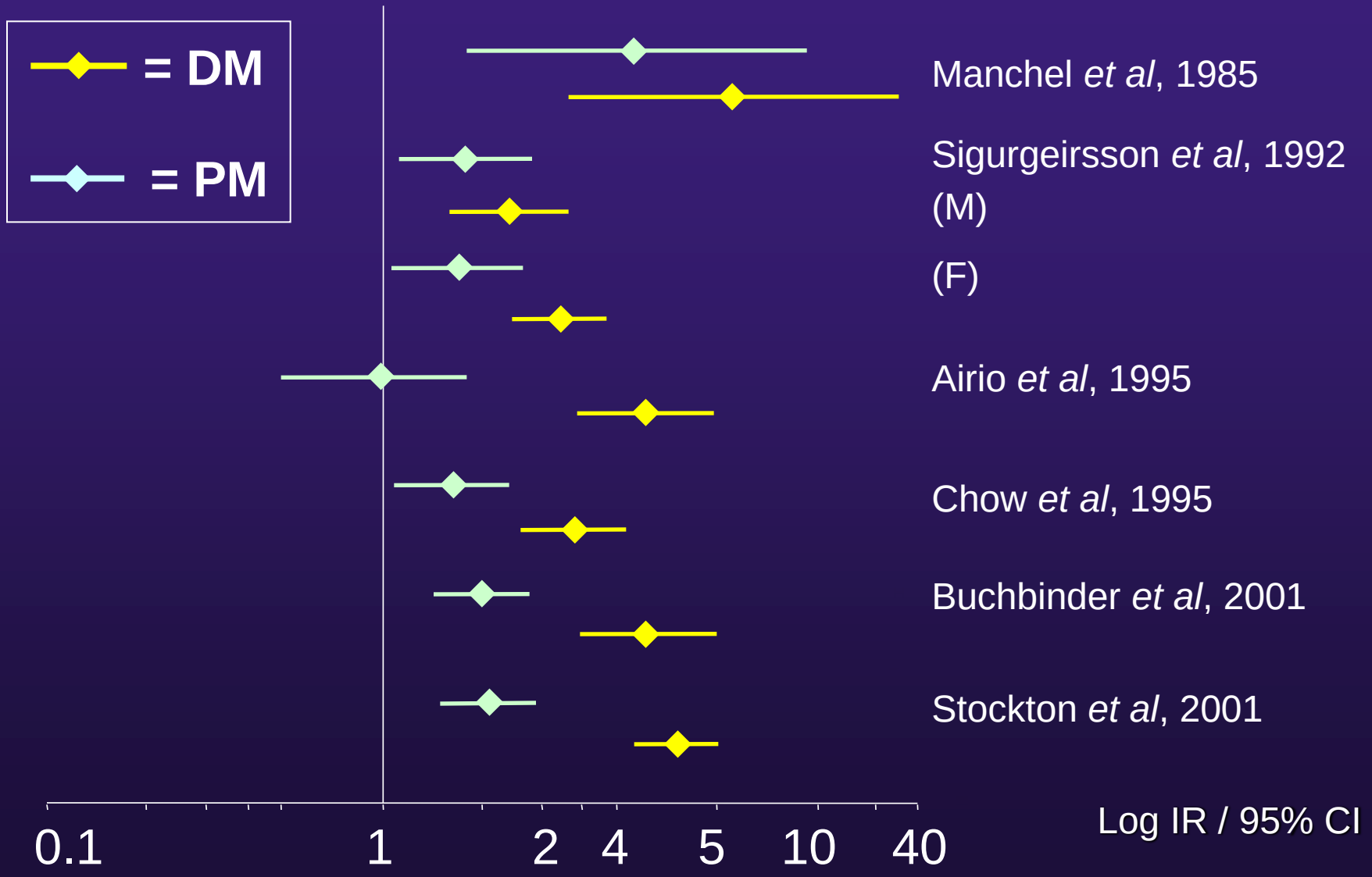
Chinoy H. *et al*, Arthritis Res Ther 2006;8:R13

Anti-Jo-1 status by smoking and HLA-DRB1*03

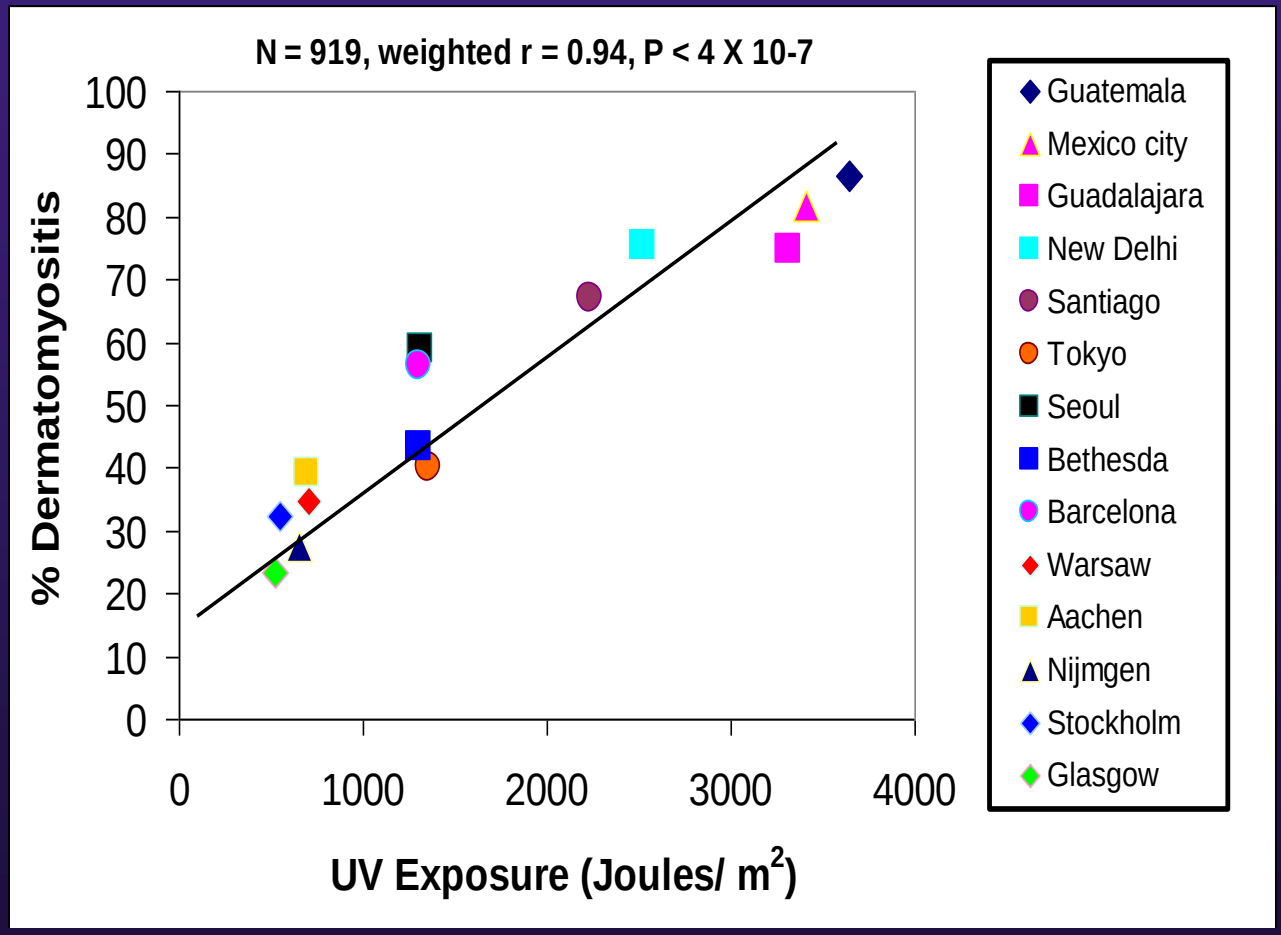


Chinoy H. *et al*, Ann Rheum Dis 2012 Jun;71(6):961-5

Population based studies of Cancer Risk in PM/DM



Global ultraviolet radiation levels predict the global proportion of DM around the world



Okada S et al. Arthritis Rheum 2003, 48:2285–2293

Infectious agents

Agent	Type	Details
Viruses	Enterovirus	Poliovirus Cocksackievirus type A/B Echovirus 11
	Retrovirus	Human immunodeficiency virus Human T-cell lymphotrophic virus
	Hepatitis	B/C Cytomegalovirus
	Parvovirus	B19
	Adenovirus	
Parasites	*Borrelia burgdorferi*	
	Toxoplasma gondii	
	Trypanosoma cruzi	

Adapted from Reed and Ytterberg, Rheum Dis Clin N Am 2002

Non-infectious agents

Agent		Exposure
Drugs, foods & dietary supplements		HMG-CoA reductase inhibitors Fibrates D-penicillamine Leuprolide acetate Hydroxyurea Adulterated rapeseed oil (toxic oil syndrome) L-tryptophan (eosinophilia myalgia syndrome) Ciguatera toxin
Biologic agents	Vaccines	DTP, MMR, BCG, influenza, hepatitis A/B
	Cytokines	Interferon-alpha Interleukin-2
	Hormones	Growth hormone
Occupational exposures		Silica, cyanoacrylate glue
Other exposures		UV light, chimerism, graft versus host disease

Adapted from Reed and Ytterberg, Rheum Dis Clin N Am 2002

Clinical features of anti-HMGCR (200/100) positive patients (45/750, 6%)

Features	
Age	52 ± 16 years
Female	58%
Statin exposure	30/45 (67%) (24/26, 92% >50 years)
CPK	9,718 ± 7,383 iu/l
Proximal weakness	96%
Irritable EMG	73%
Necrosis on biopsy	100%
Inflammation on biopsy	20%

Anti-HMGCR Ab not found in majority of statin-treated subjects, including those with self-limited statin-associated myopathy

Mammen A et al. Arthritis Rheum 2011;63:713-721

Mammen A et al. Arthritis Care Res (Hoboken). 2012;64:269-72

Eosinophilia myalgia syndrome (EMS)

- October 1989, 3 patients in New Mexico
  - Unexplained acute illness characterised by intense myalgia & peripheral blood eosinophilia, no evidence of infection/neoplastic condition that would account for findings
- November 1991, 1,543 cases reported to CDC
  - 31 deaths attributed to EMS
- L-tryptophan available over the counter since 1974, used for insomnia, depression, premenstrual symptoms
  - EMS sourced to an L-tryptophan product lot manufactured by Showa Denko
  - Administration of L-tryptophan from this lot induced inflammation of subcutaneous fascia/perimysium in mice

Acknowledgements

The patients!

The University of Manchester

Janine Lamb

Hector Chinoy

Robert G. Cooper

William Ollier

Wendy Thomson

Joanna Cobb

John Bowes

Hazel Platt

Simon Rothwell

Jo Parkes

James Lilleker

Mark Roberts

MYOGEN

Ingrid E. Lundberg

Frederick W. Miller

Peter K. Gregersen

Jiri Vencovsky

Katalin Danko

Lucy R. Wedderburn

Vidya Limaye

Albert Selva-O'Callaghan

Michael G. Hanna

Pedro Machado

Lauren M. Pachman

Ann M. Reed

Lisa G. Rider

Øyvind Molberg

Olivier Benveniste

Pernille Mathiesen

Timothy Radstake

Andrea Doria

Jan De Bleecker

Boel De Paepe

Britta Maurer

Leonid Padyukov

Terrance P. O'Hanlon

Annette Lee

MYOPROSP

Patrick Gordon

David Isenberg

Harsha Gunawardena

Parick Kiely

James Miller

Pedro Machado

EuMyoNet

- Largest IIM initiative to enable EU wide case ascertainment

Useful sites

- Dr Chinoy's twitter feed & email

@drhectorchinoy hector.chinoy@manchester.ac.uk

- MYONET

www.myonet.eu

www.euromyositis.eu

- Manchester myositis research

www.population-health.manchester.ac.uk/epidemiology/CIGMR/research/autoimmune/Autoimmunity/Myositis/

- IMACS resources including muscle biopsy video

http://www.niehs.nih.gov/research/resources/imacs/diseaseactivity/index.cfm

http://www.niehs.nih.gov/research/resources/imacs/othertools/index.cfm

Patient information

- Arthritis Research UK

http://www.arthritisresearchuk.org/arthritis-information/arthritis-information-search-results.aspx?keywords=myositis

- Fenton J. *Living with myositis—facts, feelings and future*, 2nd edn. Thoughtful Publications, London, 2006

http://www.amazon.co.uk/gp/offer-listing/0954530713

- Myositis Association (USA)

http://www.myositis.org/learn-about-myositis

- Myositis UK

http://myositis.org.uk/adult_dermatomyositis_polymyositis.htm

- Muscular Dystrophy Association (USA)

www.mdausa.org/publications/fa-myosi.html

- Muscular Dystrophy Campaign (UK)

www.muscular-dystrophy.org/how_we_help_you/publications