Advanced Stages of IBM:

What can be done to reduce disability/complications?

Namita A. Goyal, MD

THE MYOSITIS ASSOCIATION

Advanced Stages of IBM:

What can be done to reduce disability/complications?

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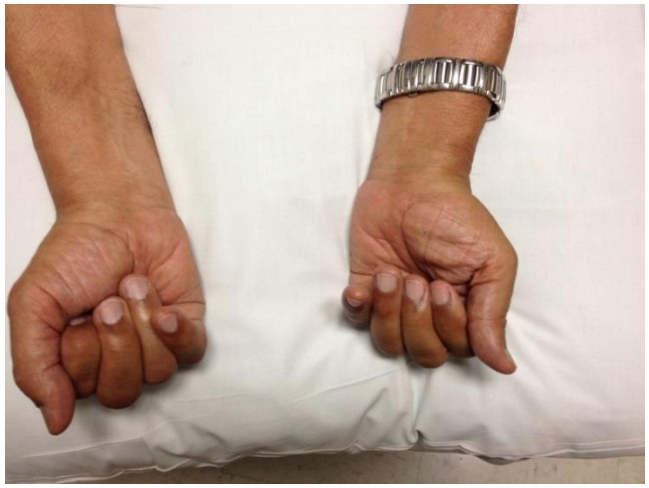
Overview of Inclusion Body Myositis

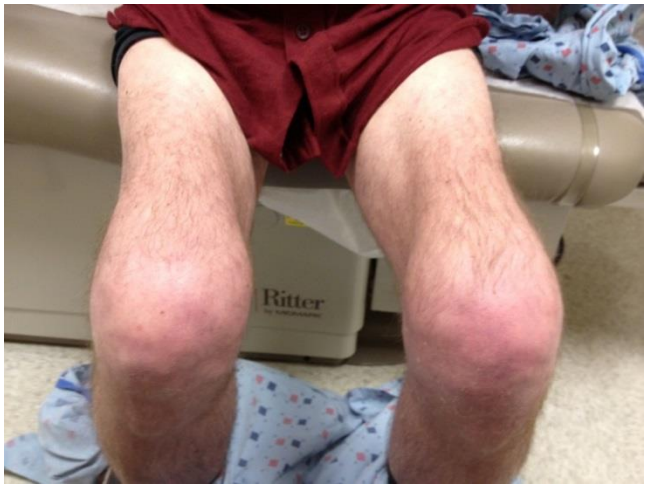
- Clinical features
- Diagnostic tests: how can they help vs be misleading?
- Progression/Management
- Multidisciplinary Care

Clinical Features

Clinical Features of IBM

- Most common acquired myopathy > age of 50 years
- Slow progressive muscle disease
  - Atrophy and asymmetric weakness
  - Predominantly affecting finger flexors, hip flexors, and knee extensors
- Males > Females
- Autoimmune vs neurodegenerative (or both?)





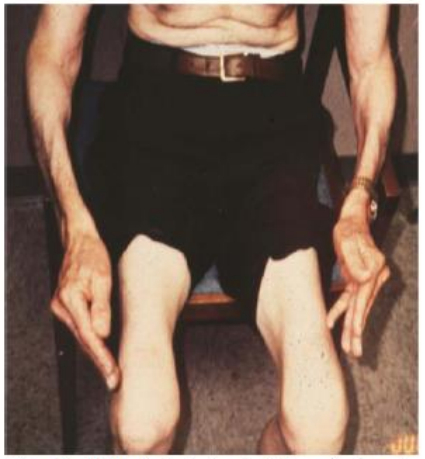


Figure 1. s-IBM patient who has typical prominent weakness and atrophy

Inclusion-body myositis

Clinical, diagnostic, and pathologic aspects

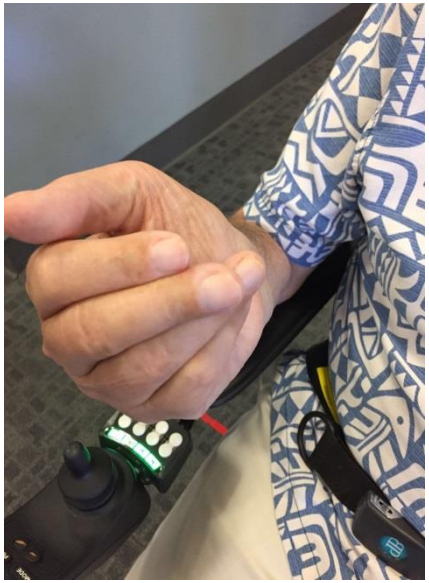
W. King Engel, MD; and Valerie Askanas, MD, PhD

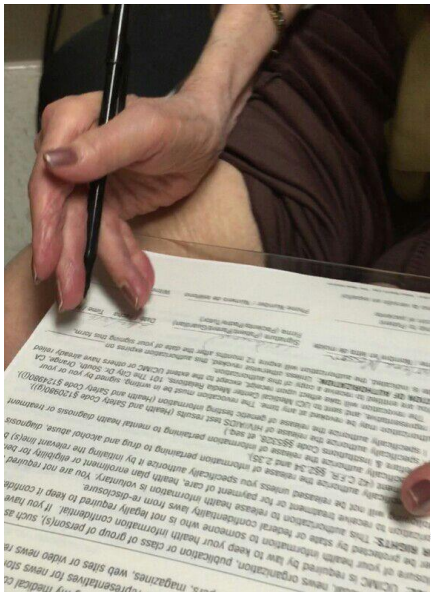
Leg Weakness: Slow progressive in IBM

- Falls
- Gait difficulty
- Arising from low seated position
- Difficulty climbing stairs
- Foot drop (dorsiflexion weakness)
- Knee buckling (quadriceps)

Grip weakness in IBM

- Grip difficulty
- Opening jars
- Manipulating keys
- Writing
- Carrying objects
- Upper arm weakness over time





Swallowing difficulty in IBM

- Frequent, embarrassing and potentially dangerous
- Initially, describe a “stuck” sensation when swallowing
- Unintended weight loss
- Higher incidence of Aspiration pneumonia
- Prevalence ranging from 40-80%

Other symptoms

- Generalized fatigue
- Mild sensory neuropathy
- Pain common and under recognized feature
- Shortness of breath, especially on exertion

Diagnostic Evaluation: Getting to the correct diagnosis

Diagnostic studies: How these tests may be helpful vs misleading in IBM?

- Muscle Enzymes (Creatine Kinase)
- Nerve conduction/Needle EMG studies
- Muscle biopsy
- Antibodies
- Muscle MRI

Creatine Kinase levels

- Normal to Moderate Elevation in many
- If Normal
  - May not think of muscle diseases
- If Markedly elevated in some (>1000 U/L)
  - May think of polymyositis or a muscular dystrophy

Table 7 Retrospective studies on the natural history of sporadic IBM

Reference	*n*	Male (%)	Age at onset (years)	Age at diagnosis (years)	Creatine kinase level (IU/l)	Patients receiving immunosuppressors (%)	Progression despite therapy (%)
Ringel *et al.*, 1987	19	79	57.8	62.9			
Lotz *et al.*, 1989	40	72.5	56.1	62.4	197	72.5	80.2
Sayers *et al.*, 1992	32	62.5	58	61	1145	87.5	46.4
Beyenburg *et al.*, 1993	36	58.3	47	53.1	279	44.4	93.75
Lindberg *et al.*, 1994	18	55.5	60.4	62.7		88.8	75
Amato *et al.*, 1996	15	86.6	58	64	698	73.3	100
Peng *et al.*, 2000	78	78.2	56.5				
Felice and North, 2001	35	65.7	64.3	70	444	49	100
Badrising *et al.*, 2005	64	67.2	57.6		417	35.9	82.6
Present study 2011	136	57.3	61	66	267	52.2	100

Brain 2011: 134; 3176–3184

Muscle Histopathology in IBM

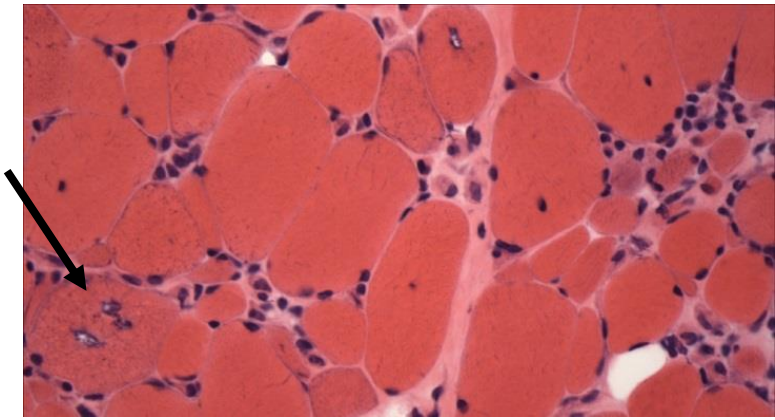
Karpati made most definitive description:
Neurology 1978 28(1): 8-17

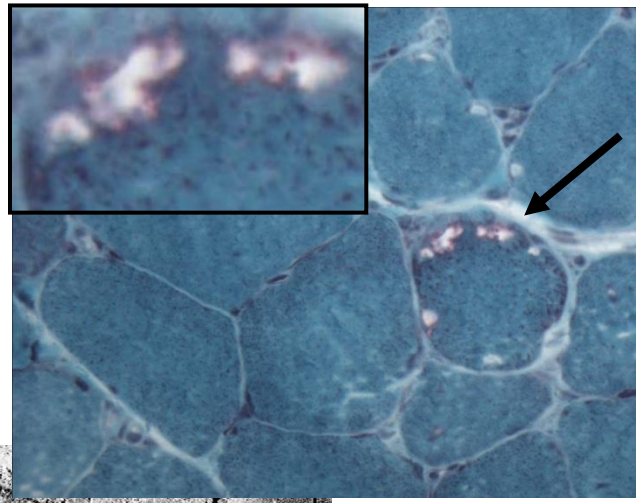
Endomysial inflammation, inflammatory cells surrounding myofibers, invasion of non-necrotic muscle fibers

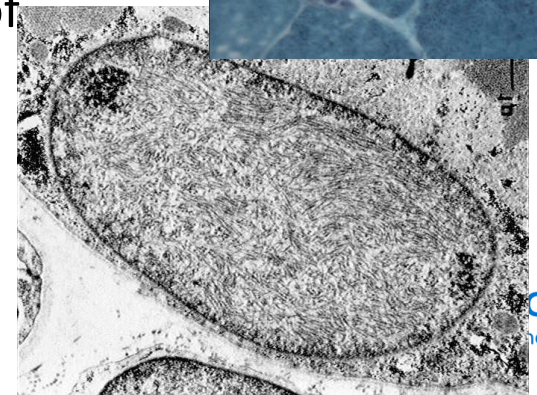
Variation in fiber size, angular fibers (neurogenic atrophy), fibrosis (chronicity)

Rimmed vacuoles in some fibers- commonly visible on Gomori trichrome- vacuoles contain degraded nuclei and membranous material

Tubulofilamentous inclusions on EM- within nuclei or in clumps in sarcoplasm suggestive of former nuclei devoid of nuclear membrane







No Rimmed Vacuoles, yet Clinical Features of IBM?

Classification at baseline and at follow up in 81 patients with endomysial mononuclear cell infiltrates with invasion of non-necrotic muscle fibers.

	RVs present	Clinical IBM	Unclassified
At presentation N (%)	49 (60.5)	14 (17.3)	18 (22.2)
At follow up N (%)	ND	29 (36)	3 (4)

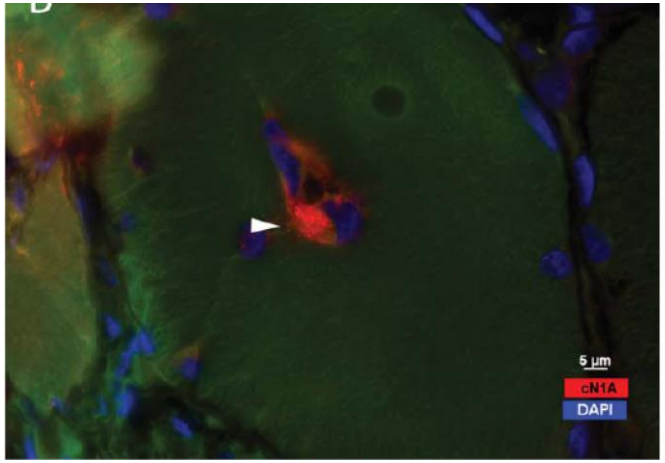
RV: Rimmed vacuoles (Patients with histopathological diagnosis of IBM with RV)
Clinical IBM: >45 yrs, FF > shoulder abductor and KE ≥ HF weakness
Unclassified: Clinical features of IBM, but not fulfilling all criteria

Nearly 40% of patients had clinical features of IBM, yet no rimmed vacuoles

van de Viekkert J et al. Neuromuscul Disorders 2015

Blood Biomarker: Anti-NT5c1A Antibody Aids in Diagnosis of IBM

- Initial reports in 2013:
  - Sensitivity 60-70%
  - Specificity 83-92%
- Subsequent reports:
  - Sensitivity 33-80%
  - Specificity 92-100%



A vacuole with NT5c1a immunoreactivity (Red) lining myonuclei (blue)
Larman HB et al. Ann Neurol 2013

Larman HB et al. Ann Neurol 2013
Pluk et al. Ann Neurol 2013

NT5C1A Antibody in IBM vs. Autoimmune diseases

Cytosolic 5′-Nucleotidase 1A As a Target of Circulating Autoantibodies in Autoimmune Diseases

THOMAS E. LLOYD, MD, PhD[1], LISA CHRISTOPHER-STINE, MD, MPH[1], IAGO PINAL-FERNANDEZ, MD, PhD[2], ELENI TINIAKOU, MD[1], MICHELLE PETRI, MD, MPH[1], ALAN BAER, MD[1], SONYE K. DANOFF, MD, PhD[1], KATHERINE PAK, MD[3], LIVIA A. CASCIOLA-ROSEN, PhD[1], and ANDREW L. MAMMEN, MD, PhD[4]

Arthritis Care Res (Hoboken). 2016 January

- Detected in 61% of 117 patients with IBM
- 5% with PM
- In Sjogrens (23%) & SLE (14%)- but no muscle weakness
- NT5C1A Ab may be helpful in differentiating IBM from PM

Muscle Imaging

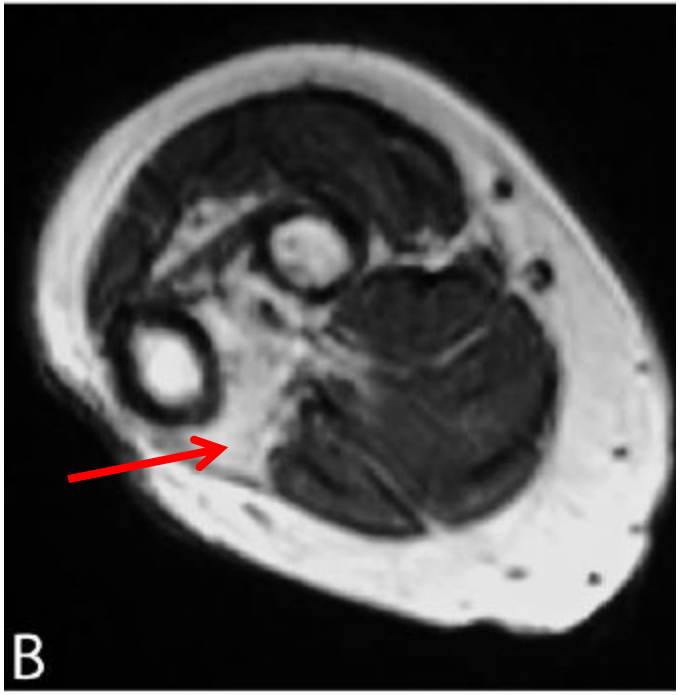
Muscle Imaging (MRI)

- Easy technique to visualize affected muscles and pattern of muscle involvement
- Detect subclinical changes
  (prior to detectable weakness on exam)
- May help measure disease progression/activity

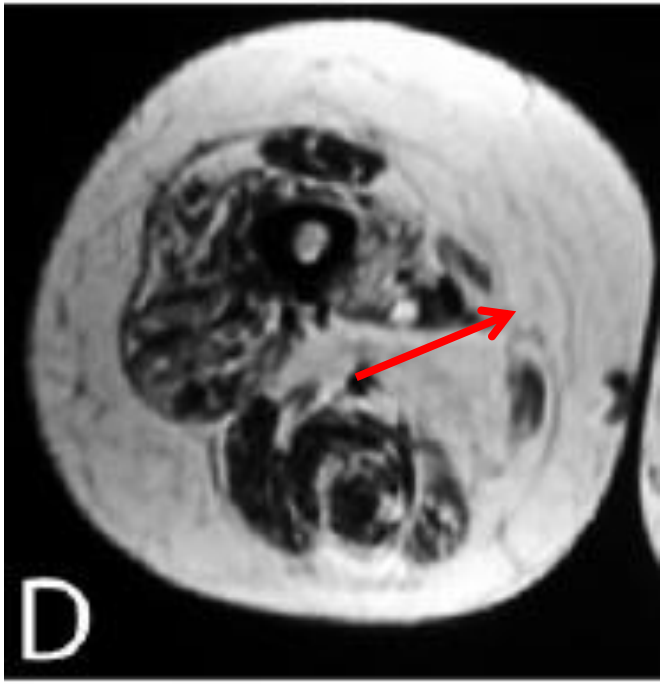
Magnetic resonance imaging of skeletal muscles in sporadic inclusion body myositis

Fieke M. Cox[1], Monique Reijnierse[2], Carla S. P. van Rijswijk[2], Axel R. Wintzen[1], Jan J. Verschuuren[1] and Umesh A. Badrising[1]

Rheumatology 2011;50:1153-1161
doi:10.1093/rheumatology/ker001



MRI forearm:
Severe fatty infiltration of Flexor digitorum profundus (FDP)

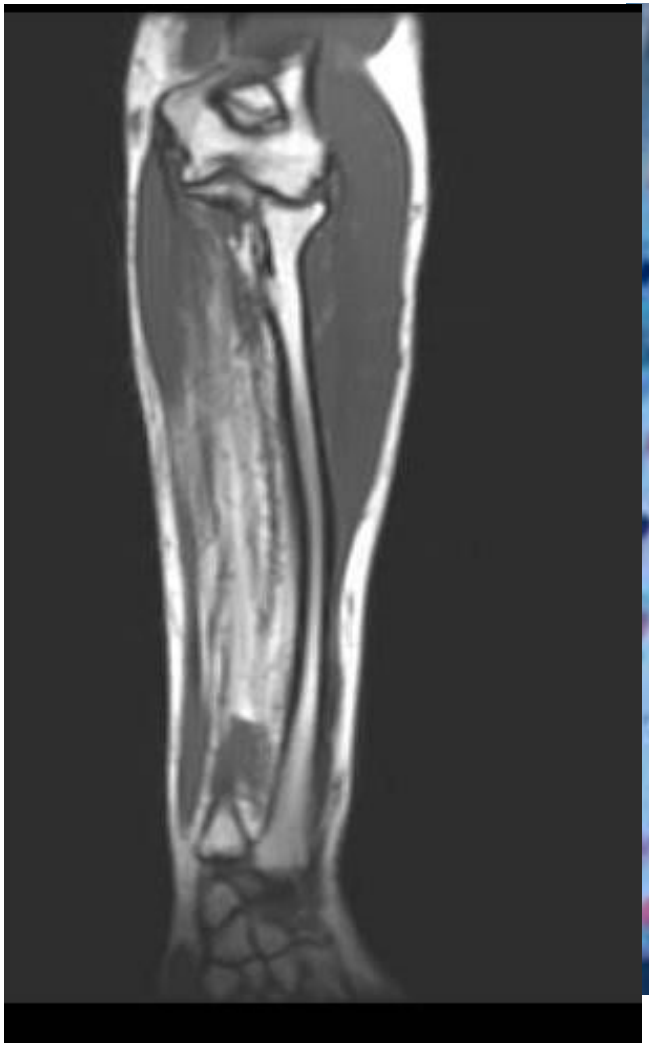


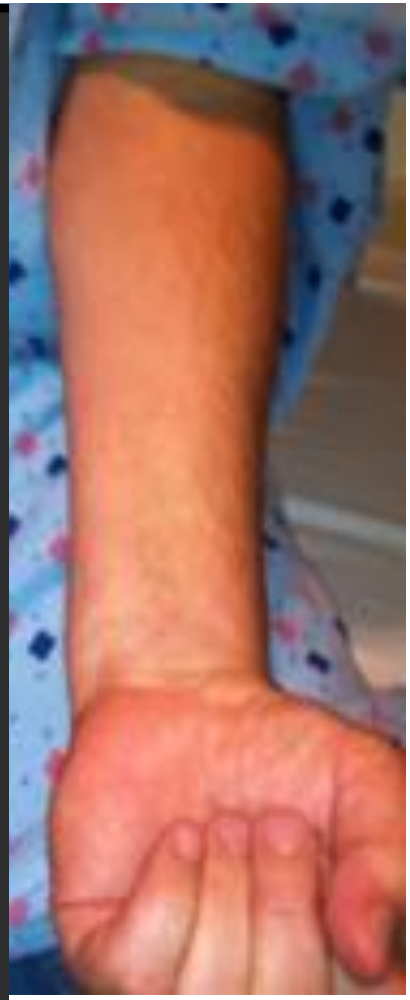
MRI Upper thigh:
Severe fatty infiltration of Vastus lateralis, relative sparing of rectus femoris and hamstrings

Muscle Imaging MRI- in sIBM

especially helpful if mild finger flexor weakness and want to confirm muscle involvement

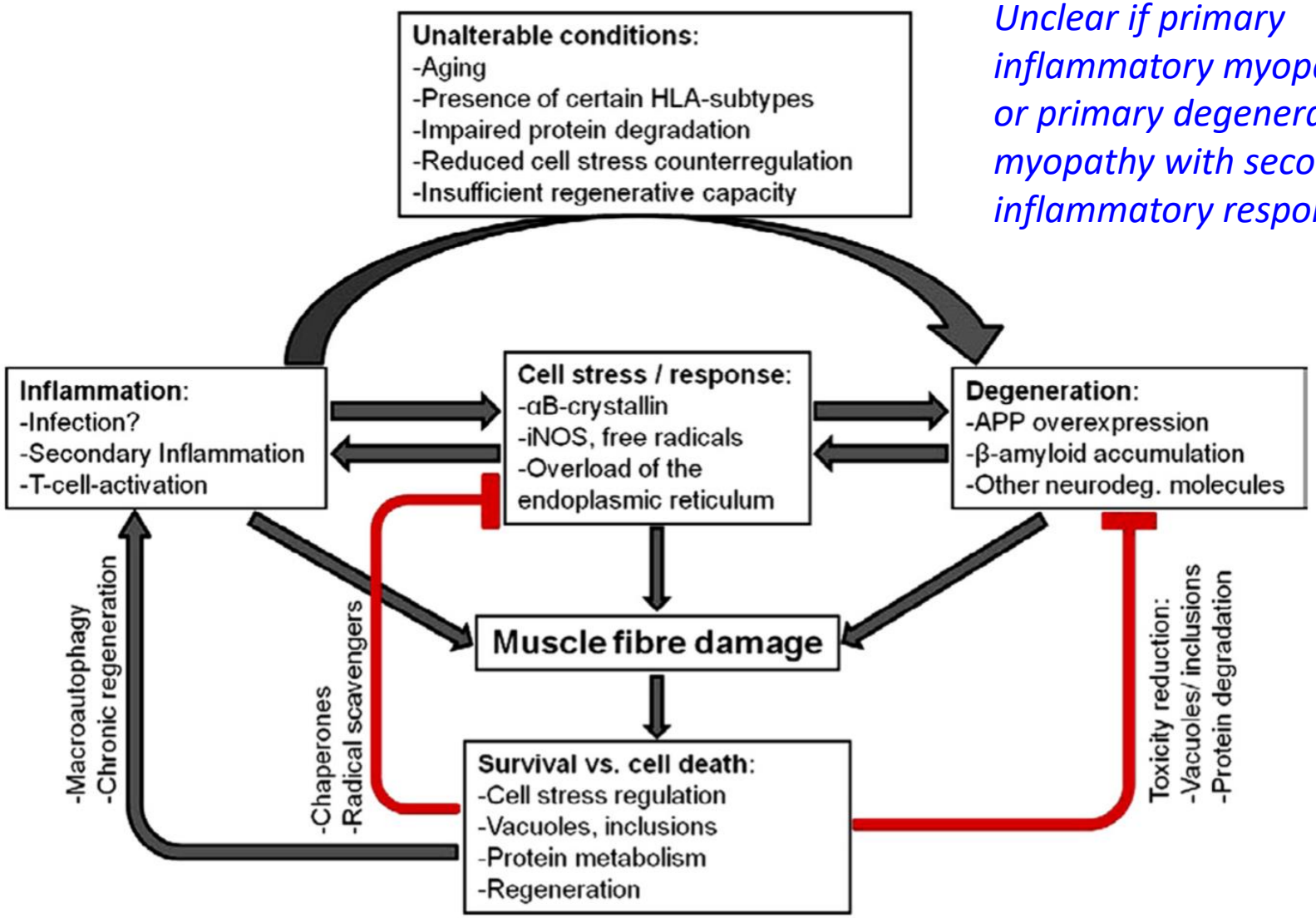
"Increased T2 signal in medial forearm flexor compartment muscles"





Management in Inclusion body Myositis

Model of Pathomechanisms in IBM



Unclear if primary inflammatory myopathy or primary degenerative myopathy with secondary inflammatory response?

Jens Schmidt, e-Neuroforum 2010

Therapeutic Agents Investigated without Sustained Improvement in IBM

1990s 2000s 2010s

Corticosteroids
Barohn et al. Neurology 1995

Methotrexate
Joffe et al. Am J Med 1993
Badrising et al. Ann Neurol 2002

Azathioprine
Joffe et al. Am J Med 1993
Leff et al. Medicine 1993

IVIg
Amato et al. Neurology 1994
Dalakas et al. Neurology 1997
Walter et al. J Neurol 2000
Cherin et al. Neurology 2002
Dobloug et al. Clin Exp Rheum 2012

Anti-T-lymphocyte globulin treatment
Lindberg et al. Neurology 2003

Oxandrolone
Rutkove et al. Neurology 2002

βINF1a (Avonex)
MSG Neurology 2001
MSG Neurology 2004

Alemtuzumab (Campath 1-H)
Dalakas et al. Brain 2009

Simvastatin
Sancricca et al. Neurol Sci 2011

Anakinra (IL1)
Kosmodis et al. J Neurol Sci 2013

Etanercept (TNF)
Barohn et al. Neurology 2006

Does Treatment with Immunotherapy make sIBM worse in the long run?

Table 5 Comparison of treated and untreated patients with sporadic IBM

Characteristics of patients	Untreated ($n = 65$)	Treated ($n = 71$)	P
Gender, male ($n = 136$)	40 (61.5)	38 (53.5)	0.39
Age at first symptoms, years ($n = 136$)	63 (57–72)	60 (53–65)	0.02
First symptoms ($n = 136$)			
Muscle weakness and swallowing difficulties	4 (6.1)	7 (10.0)	0.57
Muscle weakness only	59 (90.8)	60 (84.5)	
Swallowing troubles only	2 (3.1)	4 (5.6)	
Previous diagnosis ($n = 136$)			
None	53 (81.5)	41 (57.7)	0.002
Polymyositis	4 (6.1)	19 (26.8)	
Other	8 (12.3)	11 (15.5)	
Delay between first symptoms and sporadic IBM diagnosis, months ($n = 136$)	59 (33–86)	58 (25–98)	0.71
Status at the last visit			
Time since sporadic IBM diagnosis, months ($n = 136$)	18 (3–46)	50 (13–87)	0.001
Age, years ($n = 136$)	73 (66–79)	71 (65–76)	0.21
Muscle weakness ($n = 136$)	65 (100)	71 (100)	1.0
Severe proximal weakness[a] ($n = 136$)	28 (43.1)	36 (52.2)	0.40
Severe distal weakness[a] ($n = 136$)	25 (38.5)	28 (39.4)	1.0
Swallowing troubles ($n = 136$)	29 (44.6)	33 (46.5)	0.86
Creatine kinase, IU/l ($n = 87$)	367 (219–649)	209 (117–559)	0.11
Grip strength kgN ($n = 76$)	13.4 (11.0–17.2)	13.5 (9.0–18.0)	0.84
Walton ($n = 113$)	4 (3–6)	6 (3–6)	0.007
RMI ($n = 88$)	11 (9–13)	10 (4–11)	0.004
IWCI ($n = 71$)	50 (30–65)	40 (25–50)	0.04
Current handicap for walking ($n = 136$)			
None	20 (30.8)	13 (18.3)	0.10
One or two canes	26 (40.0)	26 (36.6)	
Wheelchair	19 (29.2)	32 (45.1)	

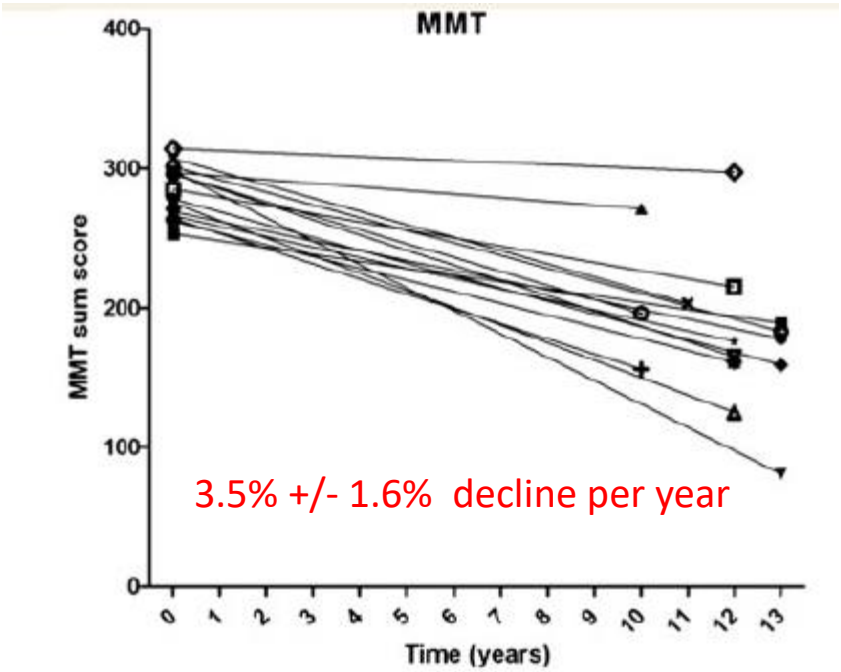
Treated group:
Less independent mobility,
Increased use of wheelchair

Brain 2011: 134; 3176–3184

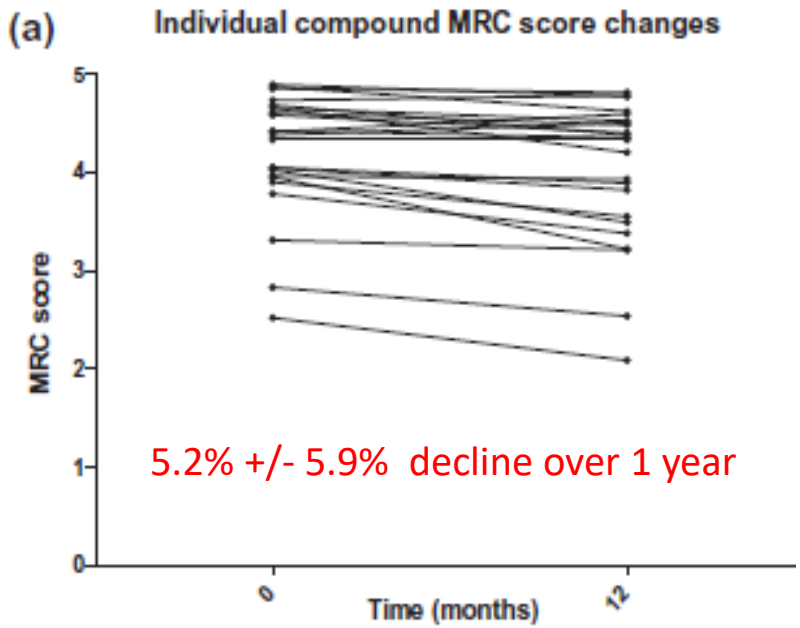
Prognosis/Progression

IBM Prognosis: Slow, gradual progression

Natural history: mean decline in muscle strength by manual muscle testing



Cox et al. Brain 2011



Cortese et al. Neuromuscul Disord 2013

Life Expectancy in sIBM: Normal

Survival seems to be <u>similar</u> to the general population

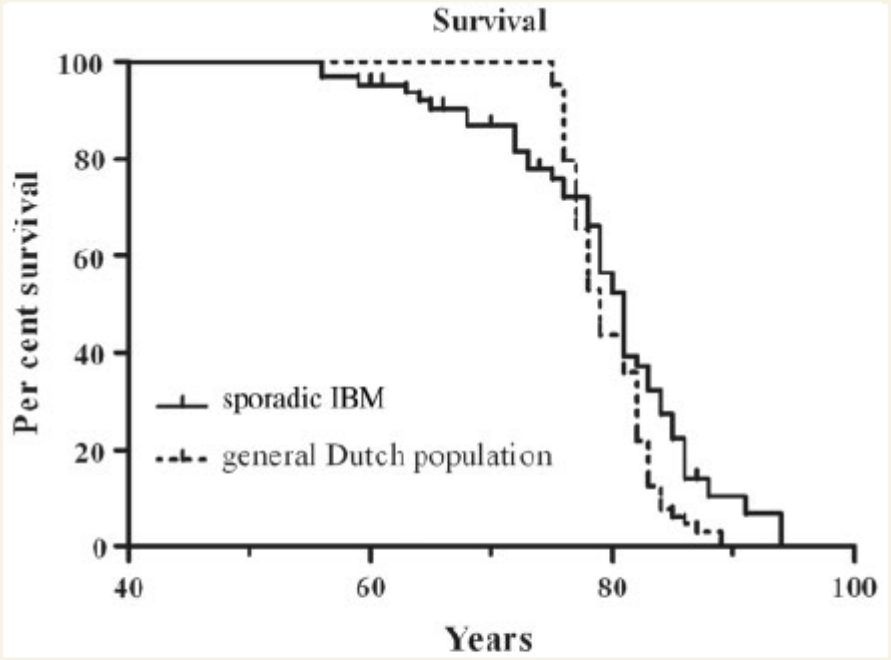


Figure 3 Kaplan-Meier curve showing a comparable survival between sIBM patients and an age- and sex-matched Dutch general population. The curve for the general Dutch population is adjusted for life expectancy for each individual sIBM patient based on the age of onset and gender.

During a 12 year follow up study:
46 of 64 patients died during follow up period
Median age at death = 81 years
In Netherlands, life expectancy 79 years

Cox et al. Brain 2011

Morbidity & Mortality in sIBM

Late Stage disease can cause very significant morbidity

Leading causes of Death:

- Respiratory (pneumonia)
- Cachexia (severe wasting with loss of weight and muscle mass)

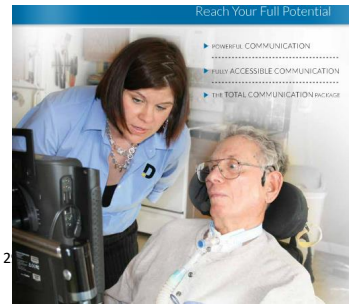
Table 2 Causes of death in the Dutch population in the age category 80–85 years and the sporadic IBM cohort

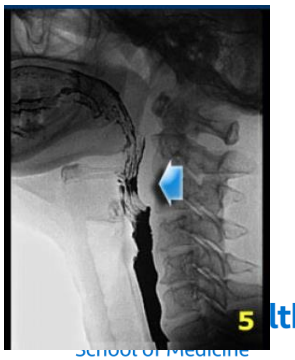
	Dutch population age category 80–84 years (%)	Patients with sporadic IBM (%)	*P*-value	Corrected *P*-value†
Infectious diseases	1.4	2.2	0.66	NS
Neoplasms	23.8	4.3	0.002	0.03*
Diseases of blood/blood-forming organs	0.4	0	0.67	NS
Endocrine/metabolic diseases	3.6	0	0.19	NS
Mental and behavioural disorders	5.6	0	0.10	NS
Diseases of the nervous system	2.8	2.2	0.80	NS
Diseases of the circulatory system (myocardial infarction)	37.7 (7.8)	19.6 (4.3)	0.01	0.16
Diseases of the respiratory system (pneumonia)	11.5 (4.4)	41.3 (28.3)	0.0001*	0.001*
Diseases of the digestive system	4.2	0	0.16	NS
Diseases of the skin	0.3	0	0.71	NS
Diseases of the bone/connective tissue	0.7	0	0.57	NS
Diseases of the genitourinary system	2.8	0	0.25	NS
Cachexia	0.1	6.5	0.0001*	0.001*
External causes of injury and poisoning	2.1	6.5	0.04	0.51
Other/uncertain	3.0	17.4		

†Corrected *P*-value is calculated with a Bonferroni correction of 14. *Significant value.

Cox et al. Brain 2011

Goal: Multidisciplinary Team Approach





Neurologist/Rheumatologist:

Subsequent visits:

- History/exam
- Muscle Strength testing
- Interval changes in:
  - Walking, Fall risk
  - Need for assistive devices
  - Function
  - Swallowing

Primary Care Physician:

- Age-appropriate health screening
- Bone density test (Vitamin D with Calcium)
- Check in with PCP if not feeling well, may not mount fever if immunosuppressed
- Vaccinations
- Help with Mood/Antidepressant?

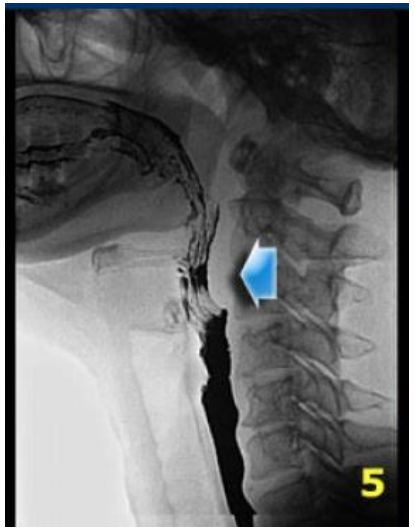
Pulmonologist/Respiratory therapist:

- Noninvasive Ventilation (BiPAP)
  - Quite beneficial in respiratory insufficiency
  - Signs of diaphragmatic weakness:
    Fatigue, muscle aches, difficulty laying flat, shortness of breath with exertion
  - Difficulty tolerating?

    Work with respiratory therapist to adjust mask/settings

Speech/Swallow Therapist:

- Difficulty swallowing/dysphagia
  - Can be leading cause of morbidity/ mortality
  - Up to 1/3 of myositis patients (esp IBM)
- Barium Swallowing evaluation
  - Can detect subclinical involvement
  - Evaluates severity
- How to help:
  - Modified diet
  - Dilatation, Crycopharyngectomy?
  - If severe, G-tube
  - Reduces risk of aspiration pneumonia
- Communication devices



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Physical/Occupational therapists:

- Risk of falls
- Adaptive equipment needs
  - Foot brace (AFO), Cane, Walker, Scooter, Wheelchair
  - Shower chair, Stair lift, Hospital bed
  - Grip devices, utensils
- Home safety evaluation – railings, grab bars
- Role of exercise
  - No pain, no gain- NOT the motto!
  - Stationary cycling, pool therapy (if safe to get in)
  - Don’t exercise to the point of pain or significant fatigue

Dietician/Nutritionist:

- Well-balanced diet, maintain weight
- If difficulty swallowing, weight loss is a concern
- With muscle atrophy, weight loss may occur
- G-tube (when severe dysphagia) – reduces risk of aspiration
  - Maintain calories and weight
  - Helpful for pills
  - Hydration
- Constipation (common), esp in impaired mobility

Social Worker:

- Care giving resources
- Disability/Insurance
- Home health services
- Support groups
- Psychologists/psychotherapists

In Summary:
Multidisciplinary Care Improves Quality of Life

- **Mobility**
  - Assistive devices (AFOs, cane, braces, walker, wheelchair)
  - Risk of falls
- **Dysphagia**
  - Diet modification
  - Dilation, cricopharyngectomy?
  - Gastrostomy tube, Risk of aspiration pneumonia
- **Respiratory insufficiency**: Noninvasive ventilation (BiPAP)
- **Adaptive Equipment**
  - Shower chair, stair lift, safety rails, hospital bed
  - Home safety evaluations and bathroom modifications
- **Role of Exercise**: May slow progression

Thank you!

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