

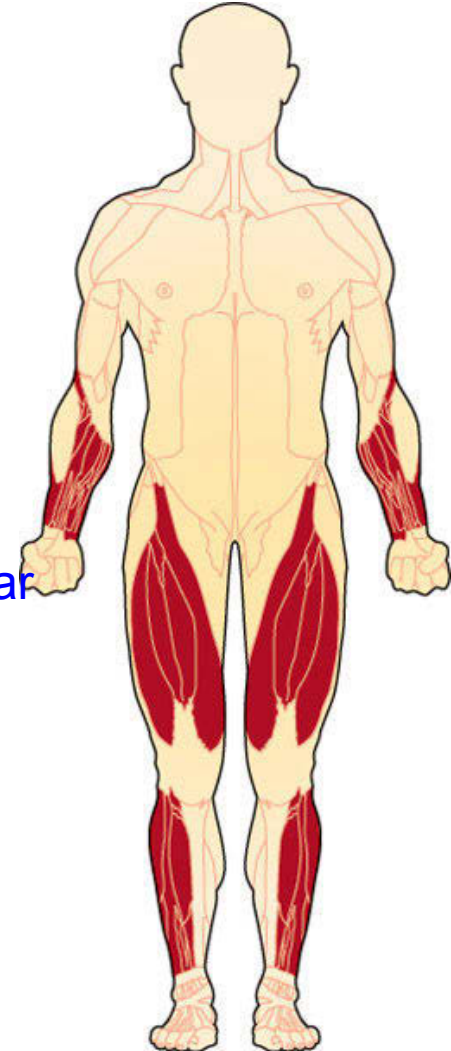
Current concepts in the management of Inclusion Body Myositis

16th Nov 2014

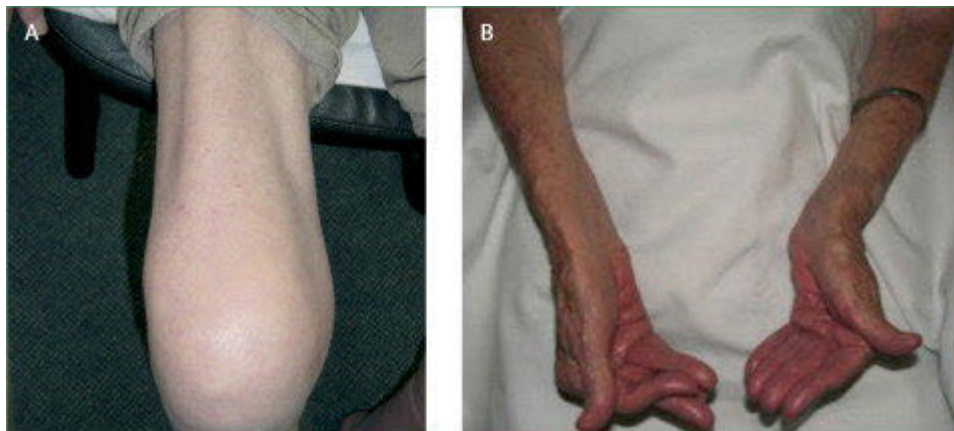
Christina Liang
Royal North Shore Hospital

IBM - characteristics

- In > 50 years
- Diagnostic delay
- “Slowly progressive”
 - Asymmetric
 - Deep finger flexors, quadriceps, lower leg muscles
 - » ...Nursing home, unable to swallow...
 - Decline in quantitative muscle testing by 5.4% \pm 3.5%/ year
 - Faster in men, late-onset disease
 - Time to wheelchair ~ 15 years
 - Normal life expectancy
 - But causes of death: respiratory dysfunction, aspiration, dysphagia, cachexia
- Coexisting autoimmune+degenerative changes



<http://mda.org/disease/inclusion-body-myositis/overview>



<http://www.thelancet.com/journals/laneur/article/PIIS1474442207701710/images?imageId=qr1>



An update

IN TERMS OF DIAGNOSTICS

Table 1. European Neuromuscular Centre inclusion body myositis research diagnostic criteria 2011

Diagnostic subgroup	Clinico-pathologically defined IBM	Clinically defined IBM	Probable IBM
Clinical features			
Duration of weakness > 12 months	X	X	X
Age at onset > 45 years	X	X	X
Creatine kinase ≤ 15 times ULN	X	X	X
FF weakness > SA weakness and/or KE weakness ≥ HF weakness	X	–	–
FF weakness > SA weakness; KE weakness ≥ HF weakness	–	X	–
FF weakness > SA weakness or KE weakness ≥ HF weakness	–	–	X
Pathological features			
Endomysial inflammatory infiltrate	X	At least one, but not all of the four pathological features	At least one, but not all of the four pathological features
Rimmed vacuoles	X	At least one, but not all of the four pathological features	At least one, but not all of the four pathological features
Protein accumulation ^a or 15–18 nm filaments	X	At least one, but not all of the four pathological features	At least one, but not all of the four pathological features
Upregulation of MHC class I	–	At least one, but not all of the four pathological features	At least one, but not all of the four pathological features

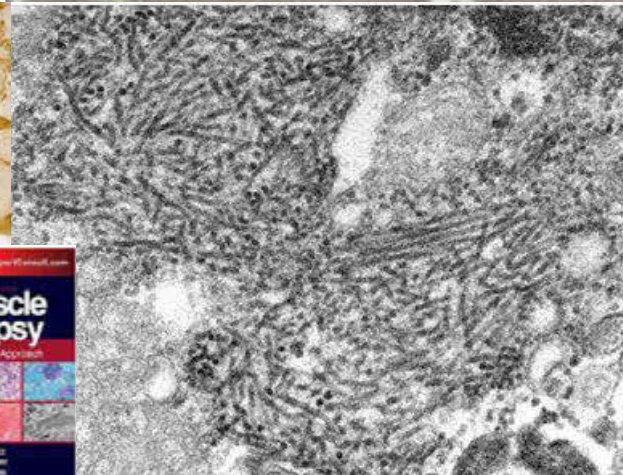
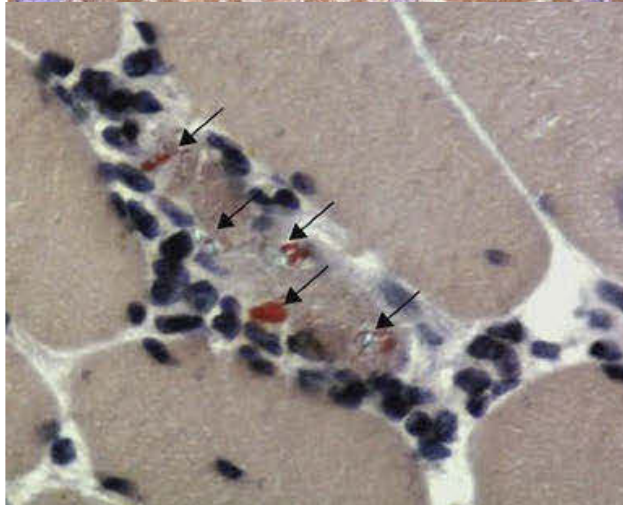
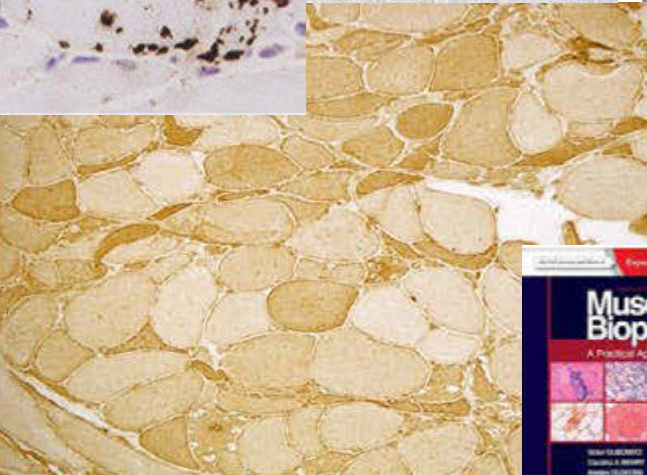
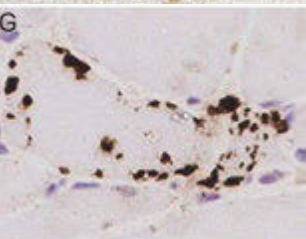
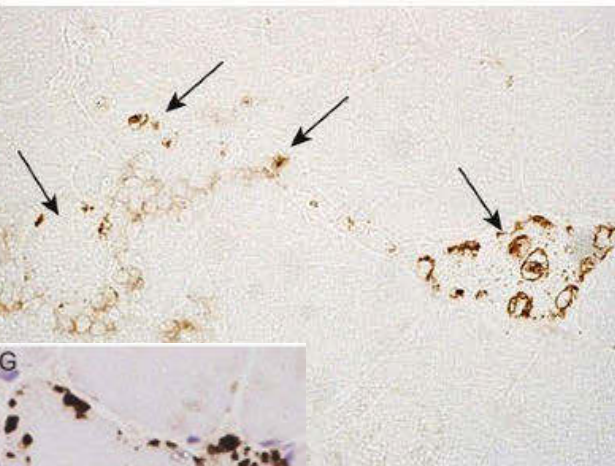
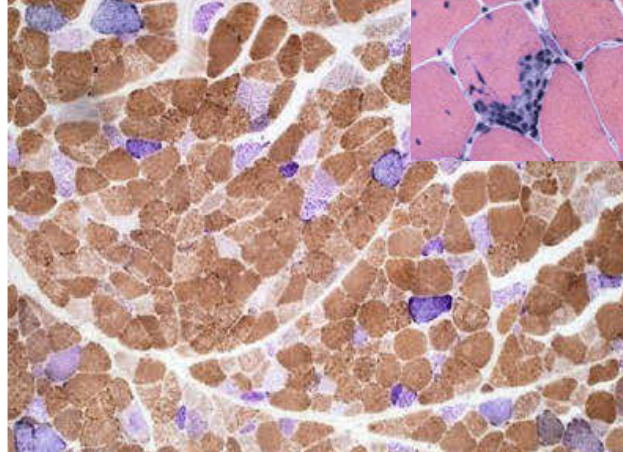
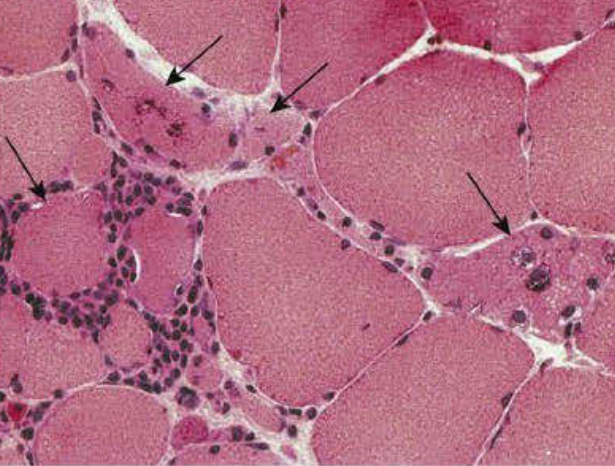
FF, finger flexion; HF, hip flexion; IBM, inclusion body myositis; KE, knee extension; MHC class I, major histocompatibility complex class I; SA, shoulder abduction; ULN, upper limit of normal.

^aDemonstration of amyloid or other protein accumulation by established methods (e.g., for amyloid Congo red, crystal violet, thioflavin T/S, for other proteins p62, SMI-31, TDP-43).

Adapted with permission from [38²²].

Sporadic inclusion body myositis: new insights and potential therapy

27 • Number 5 • October 2014



- **With rimmed vacuoles:**
 - **MHC class 1 + p62 staining pattern**
 - in vacuolated + non-vacuolated fibres, strongly stained, discreet, clearly delineated, round/ angular
 - subsarcolemmal, perinuclear and perivacuolar
 - Sensitivity 93%
 - Specificity 100%
- **Without rimmed vacuoles**
 - **COX-/SDH+**
 - Sensitivity 100%
 - Specificity 73%
 - (vs PM, DM)
- **p62 staining pattern**
 - excellent specificity, low sensitivity
- **Absence of COX-/SDH+ fibres**
 - should doubt IBM as diagnosis

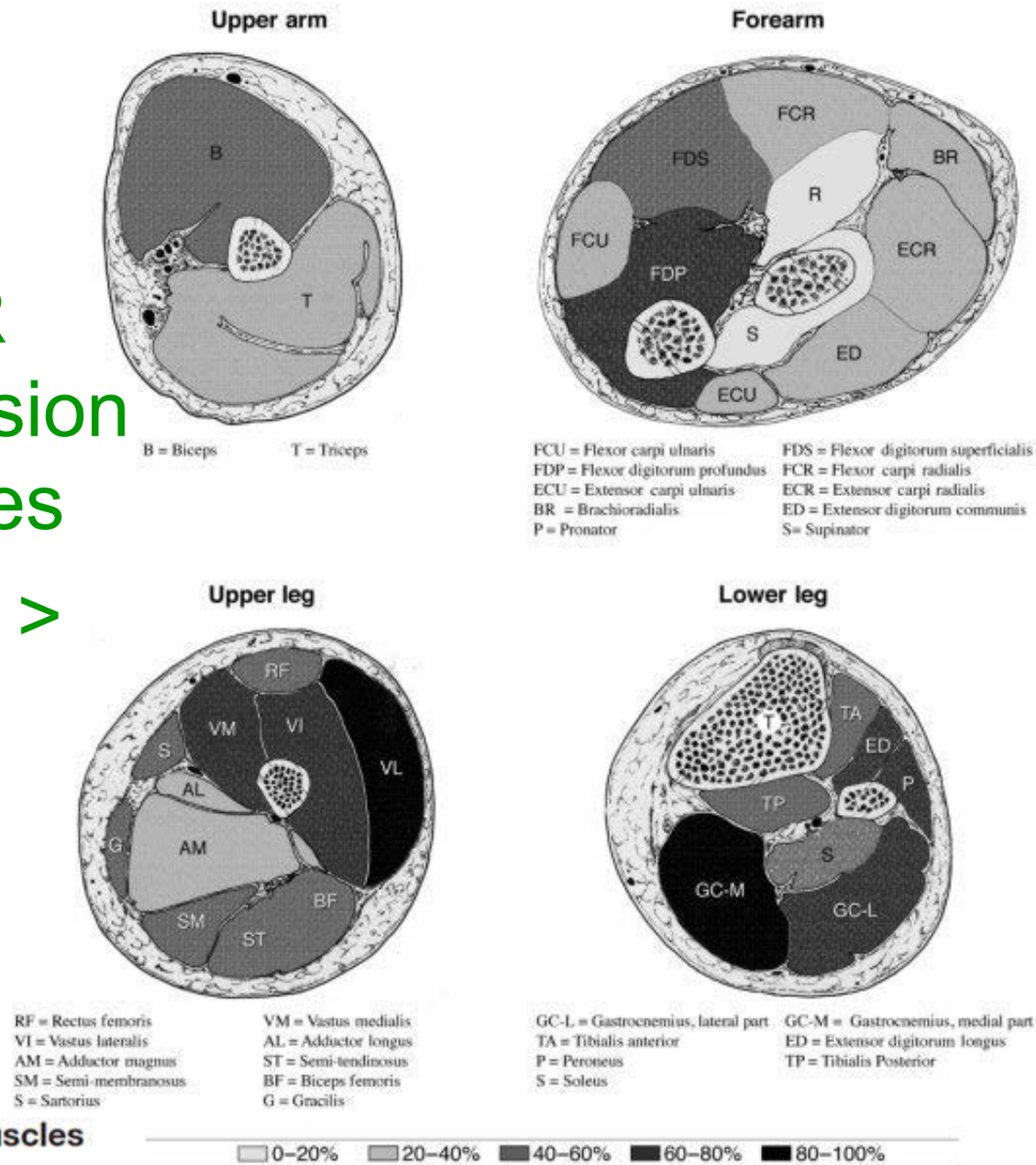
A retrospective cohort study identifying the principal pathological features useful in the diagnosis of inclusion body myositis

BMJ open 2014

Stefen Brady,¹ Waney Squier,² Caroline Sewry,^{3,4} Michael Hanna,¹ David Hilton-Jones,⁵ Janice L. Holton⁶

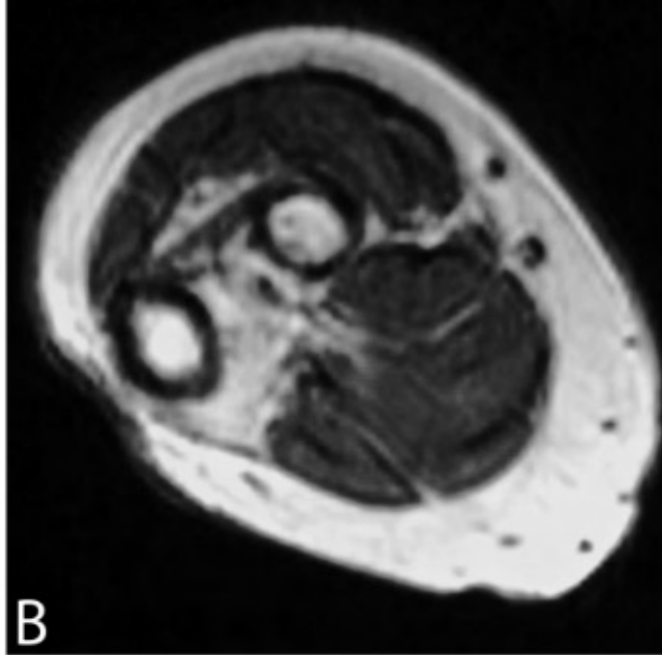
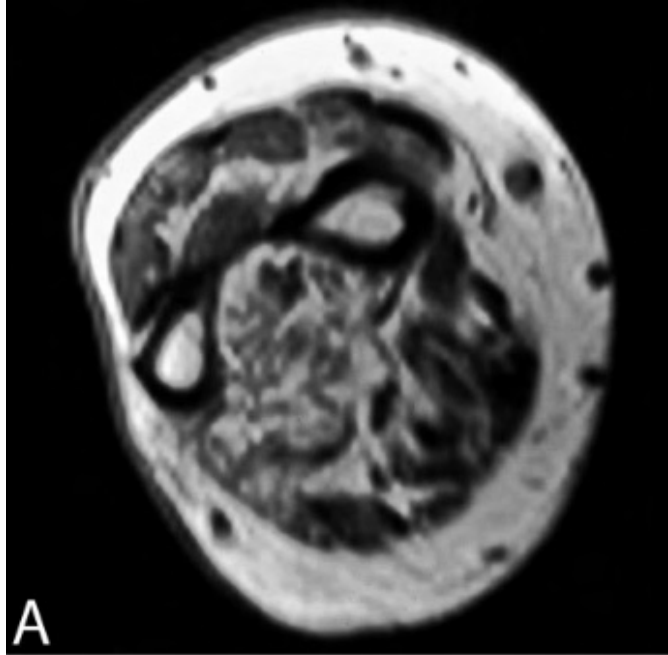
MRI study

- N = 32
- 1.5T MRI, STIR (short tau inversion recovery) images
- Fatty infiltration > inflammation



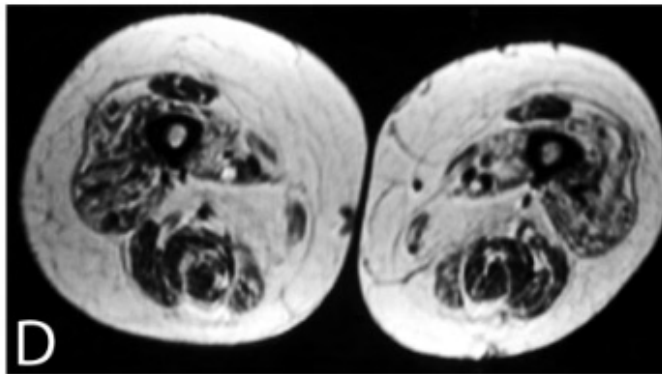
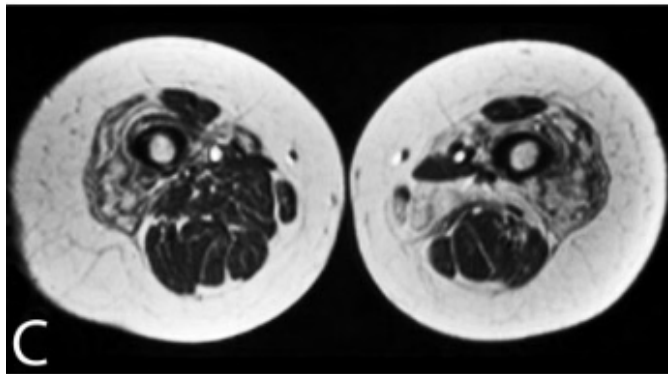
Magnetic resonance imaging of skeletal muscles in sporadic inclusion body myositis

Moderate
fatty
infiltration
of FDP



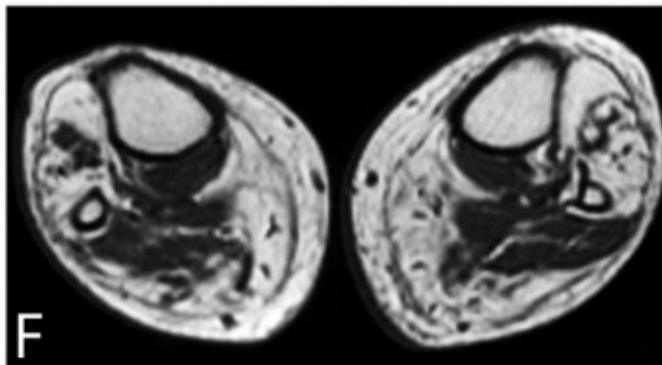
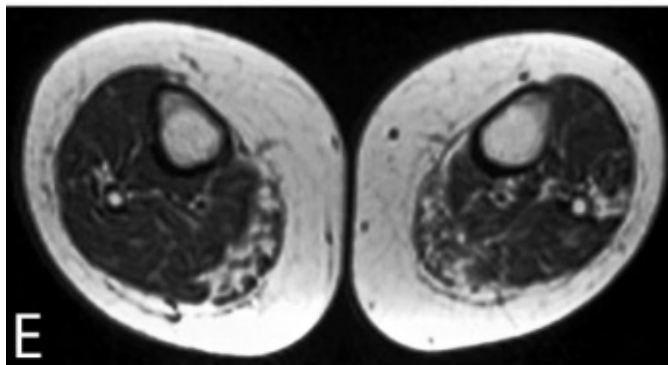
Severe
fatty
infiltration
of FDP

Severe
fatty
infiltration
of vastus,
sparing
rectus,
hamstrings
,adductors



Severe
fatty
infiltration
of vastus,
sparing
rectus

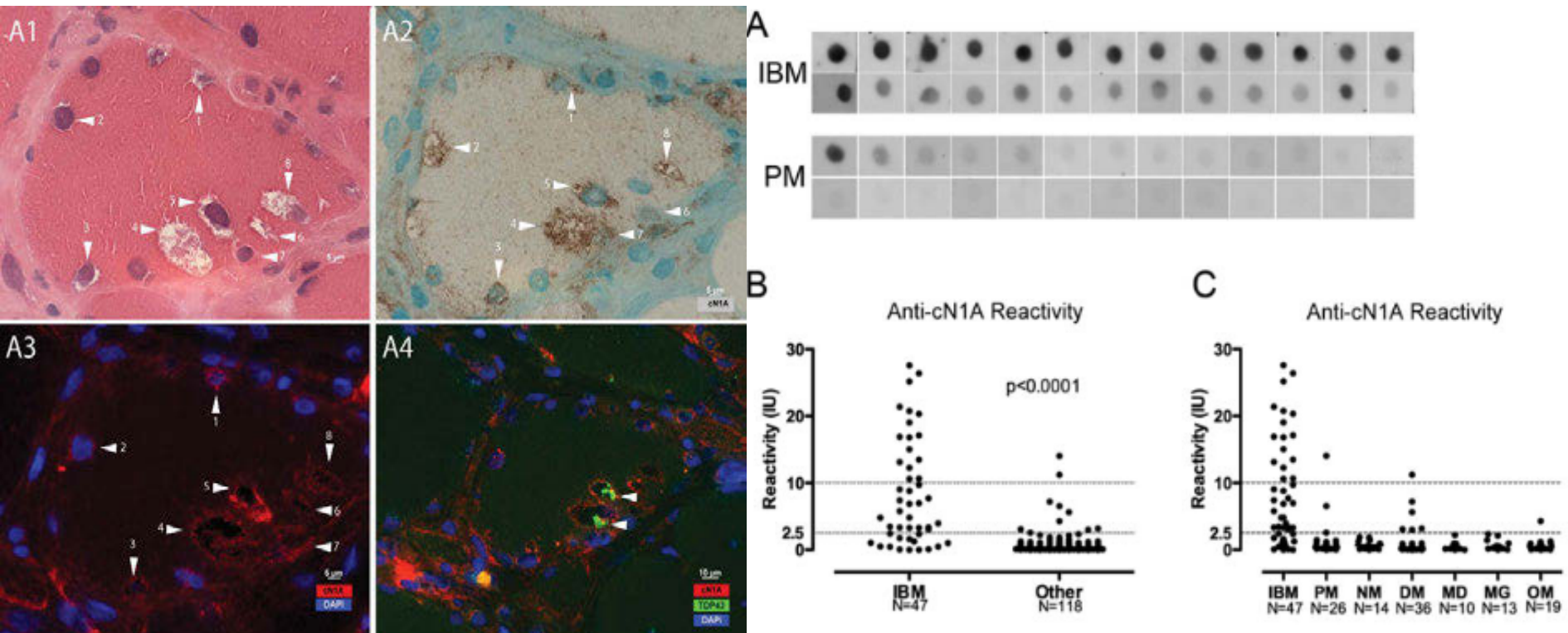
Moderate
fatty
infiltration
of medial
gastroc



Severe
fatty
infiltration
of medial
gastroc

Diagnostics

- Cytosolic 5' nucleotidase 1A (cN1A)
 - Moderate reactivity of anti-cN1A antibodies -> sensitivity 70%, specificity 92%
 - ELISA Kit IgG~ \$1150.6 for 96 wells (research use)
 - for 32 subjects x 3 runs ~\$35 / test



Cytosolic 5'-nucleotidase Autoantibodies

- Anti-cN1A
 - Found in areas of myonuclear degeneration, rimmed vacuoles
- Anti-cN1A IgG
- Anti-cN1A IgG, IgM, IgA
 - Similar sensitivities 49-53%
 - Specificities (94-96%)
 - Diagnostic sensitivity 76%

CYTOPLASMIC 5'-NUCLEOTIDASE AUTOANTIBODIES IN INCLUSION BODY MYOSITIS: ISOTYPES AND DIAGNOSTIC UTILITY

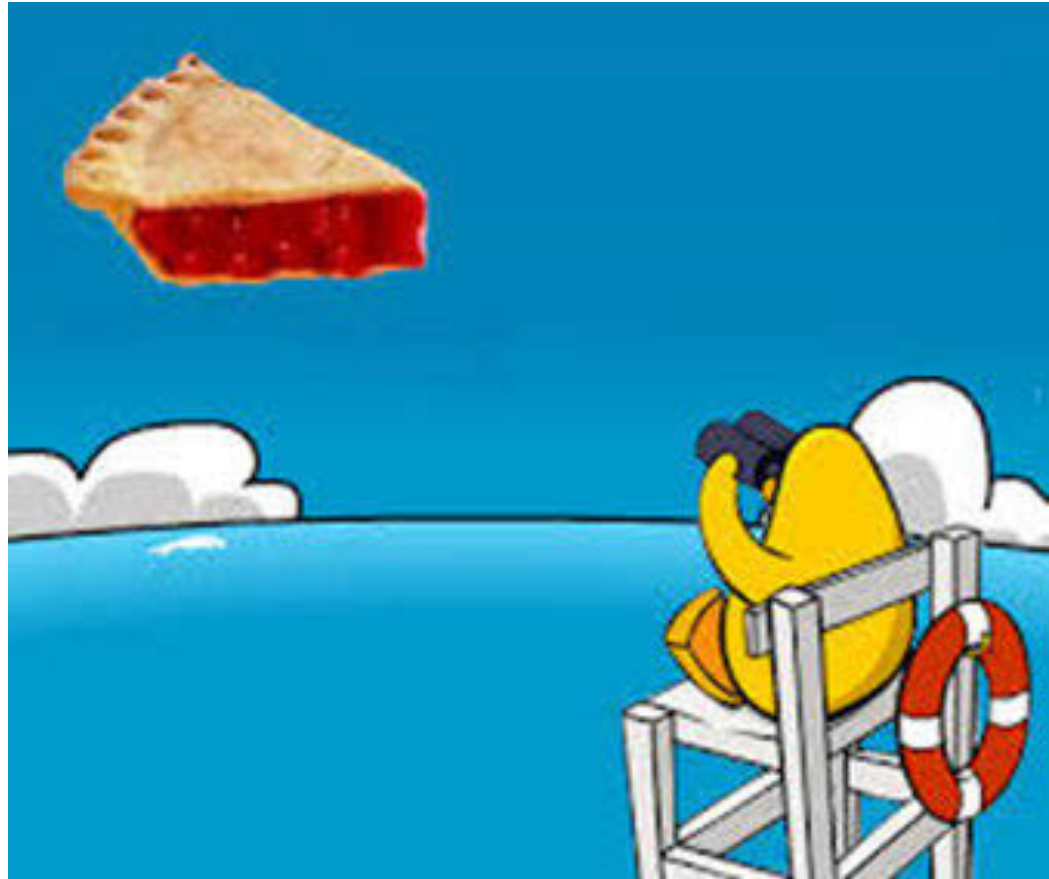
STEVEN A. GREENBERG, MD

Department of Neurology, Brigham and Women's Hospital and Children's Hospital Informatics Program, Harvard Medical School and Harvard-MIT Division of Health Sciences and Technology, Boston, Massachusetts, USA

Accepted 4 February 2014

An update

ON THERAPY

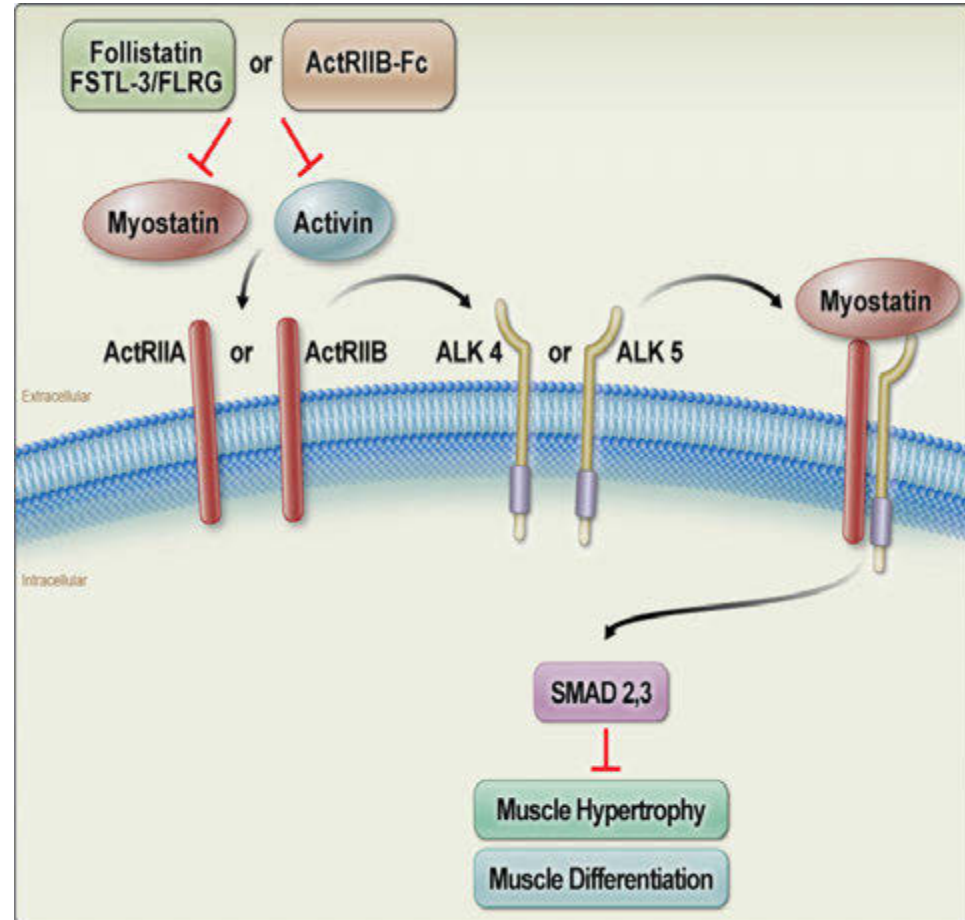


“Treatment resistant”

- **Corticosteroids**
 - Occasional patient with transient, mild improvement **early in disease course**
 - Progressive resistance over 3-6 years
- **Immunoglobulin**
 - Earlier report
 - Not subsequently
- **Oxandrolone**
 - Borderline significant effect for whole-body strength
- **Ineffective**
 - Beta-interferon 1a – standard & high dose
 - Methotrexate
 - Etanercept
 - Alemtuzumab
 - Lithium chloride – inducing autophagy

Myostatin

- Secreted protein
 - Transforming growth factor beta (TGF β) family
 - Activated when cleaved by metalloproteinase
- Binds **activin receptor type IIB** (ActRIIB)
 - >SMAD 2, 3 activation
 - Transcription factors
 - Phosphorylation of SMAD2, 3 ->
- Inhibits myoblasts proliferation
 - Inhibits differentiation into mature muscle fibres

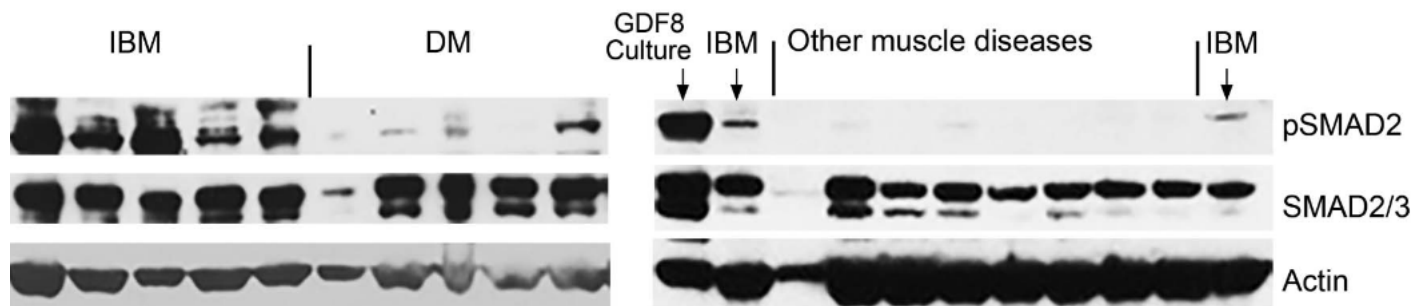


Bimagrumab/ BYM338

- Fully human monoclonal Ab
 - Binds with high affinity to ActRIIB-R
 - Blocks myostatin binding
- Other proposed uses:
 - Sarcopenia from ageing
 - Cachexia from cancer
 - Muscle wasting in mechanical ventilated patients

Bimagrumab/BYM338 – Pilot study

- Muscle **SMAD2/3 phosphorylation**
 - N= 50 (sIBM = 17, DM = 5, PM = 7, toxic myopathy = 4, mito = 4, idiopathic = 3, denervation atrophy = 2, DM1 = 1, nemaline = 1, distal myopathy = 1)
 - Higher in sIBM > other muscle diseases
 - IBM ↑27.4X (p = 0.003)
 - Inflammatory muscle disease ↑2.5x
 - Non-inflammatory muscle diseases ↑1.7X



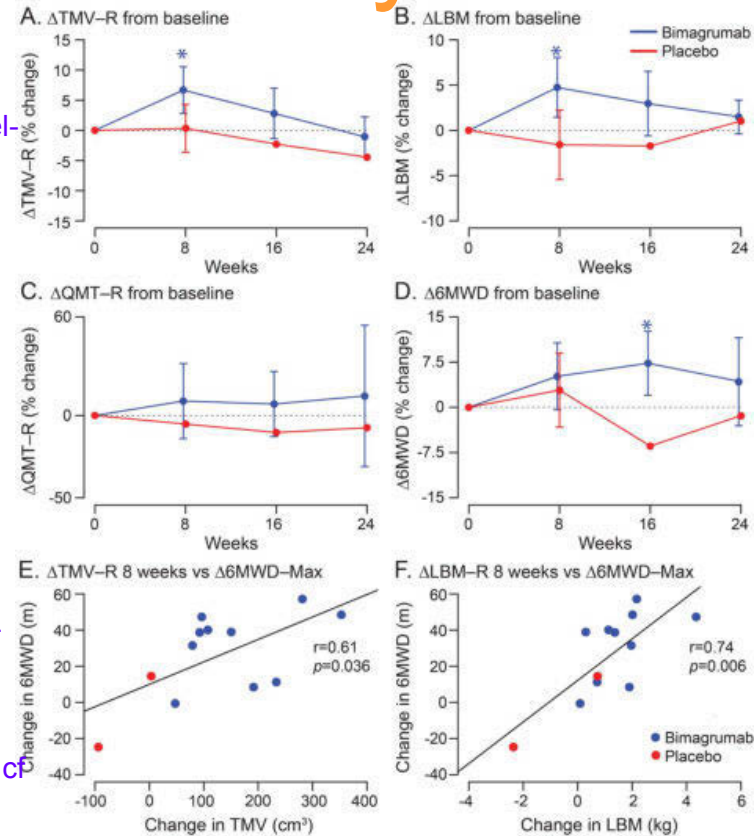
Anthony A. Amato, MD
Kumaraswamy
Sivakumar, MD
Namita Goyal, MD
William S. David, MD,
PhD
Mohammad Salajegheh,
MD
Jens Praestgaard, PhD
Estelle Lach-Trifilieff,
PhD
Anne-Ulrike
Trendelenburg, PhD
Didier Laurent, PhD
David J. Glass, MD
Ronenn Roubenoff, MD,
MHS
Brian S. Tseng, MD, PhD
Steven A. Greenberg, MD

Treatment of sporadic inclusion body
myositis with bimagrumab

Neurology. 2014 Nov 7 Epub

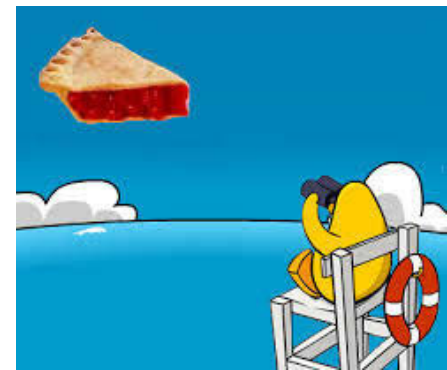
Bimagrumab – Pilot study

- N=14 (11 on Rx, 3 on placebo; age 42-78; ENMC criteria - definite)
 - 8-week randomised, placebo-controlled, double-blind, parallel-arm, proof of concept study
 - 24-week observation phase
- Single 30mg/kg dose iv
 - Inhibits (ActRII A and B)
 - Thought saturating ActRII for ~ 8 weeks
- At 8 weeks:
 - ↑ **Thigh muscle volume** (R↑ 6.5%, L ↑ 7.6%,, $p < 0.03$)
 - 1.5T MRI – proton density
 - At 24 weeks – remains non-significantly ↑
 - ↑ **Lean body mass** (↑ 5.7%, $p = 0.014$)
 - DXA
 - Isometric muscle strength
 - QMT – non-significant increase in all muscle groups except L quad, R hamstrings
 - Timesd up and go – no difference
 - **6 minute walk distance test**
 - Peaked at 16 weeks, (↑ 14.6%, $p = 0.008$); at 24 weeks ↑ 5.7% cf placebo
- SE: mild acne, fleeting muscle contractions, mild diarrhoea



Treatment of sporadic inclusion body myositis with bimagrumab

Neurology. 2014 Nov 7 Epub



Follistatin gene (FS344)

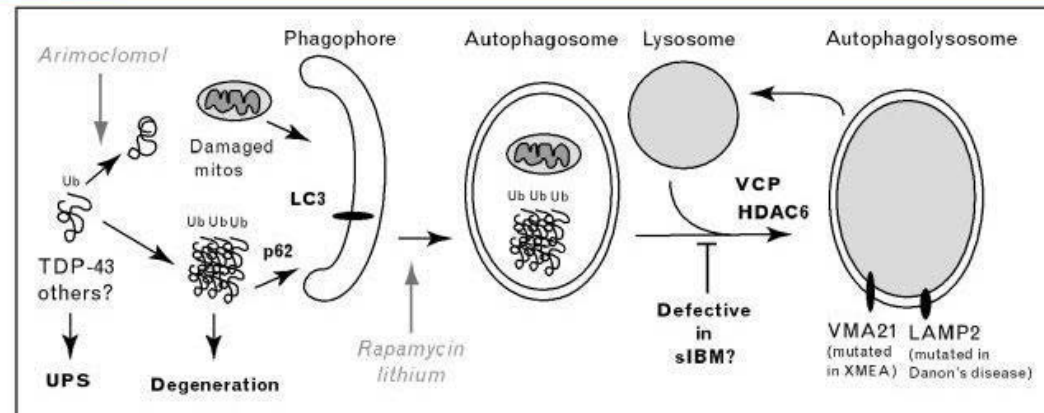
- Adeno-associated virus as vector
- Intramuscular injection
- Open-label N = 9
 - Low, medium, high doses
 - Bilateral quadriceps
- Single injection - ? To long-term expression of follistatin gene

Sporadic inclusion body myositis: new insights and potential therapy

Upregulation of heat shock response

- **Arimoclomol**
 - Heat shock protein 70 inducer
 - Amplifies heat shock protein expression (chaperones)
 - Helps protein dyshomeostasis, defective autophagy
 - Helps prevent accumulations of misfolded proteins
 - Tried in ALS
- **N= 16, randomised, double-blind, placebo-controlled trial**
 - 100mg orally tds for 4 months
 - 8 mo blinded follow-up
- **Trend of slower decline in muscle strength, and physical function**

Medscape



Sporadic inclusion body myositis: new insights and potential therapy

An update

ON THE “UP-KEEP”

Sleep disordered breathing

- N=16 (10M, BMI 28.5+/-4kg/m²)
 - No correlation between:
 - Respiratory function impairment
 - Sleep disordered breathing
 - Severity of peripheral muscle weakness
 - Sleep disordered breathing observed in all patients tested – irrespective of daytime respiratory function
 - Asymptomatic impairment of respiratory function - common
 - Consider sleep study routinely sIBM patients
- N= 13 (7M, >10 yrs, mean age 66.2+/-11.1)
 - Lower sleep efficiency, more awakenings, increased nocturnal time awake
 - 7 of 13 had sleep disordered breathing

Sleep disordered breathing and subclinical impairment of respiratory function are common in sporadic inclusion body myositis

Pedro M. Rodríguez Cruz^{a,b}, Merrilee Needham^{b,c}, Peter Hollingsworth^d, Frank L. Mastaglia^{b,c}, David R. Hillman^{c,*}

Sleep disordered breathing in a cohort of patients with sporadic inclusion body myositis

Giacomo Della Marca^{a,*}, Cristina Sancricca^a, Anna Losurdo^a, Chiara Di Blasi^a, Chiara De Fino^a, Roberta Morosetti^a, Aldobrando Broccolini^a, Elisa Testani^a, Emanuele Scarano^b, Serenella Servidei^a, Massimiliano Mirabella^a



Exercising consistently - safe

- Treadmill, exercise bikes
- Physiotherapist
- Exercise physiologists
- 16-week home-exercise program
 - 2x/day, patient-tailored ex
 - N=7 (2 cane, 2 scooter)
 - Sit-to-stand, biceps curl, shoulder press, heel lifts, isometric vastus medialis ex, ankle dorsiflexion
 - Improved in all muscle group strength
 - Time to climb 1 flight of stairs + walk 30m
- Aerobic exercise program
 - N= 7 for 12 weeks
 - Stationary cycle ergometer
 - Isometric, isotonic ex of UL, LL
 - Improved aerobic capacity, muscle strength
 - No change in grip or KE strength
- Moderate to low intensity strength training + vascular occlusion
 - Increase in muscle strength and size

The Effectiveness of an Individualized, Home-Based Functional Exercise Program for Patients With Sporadic Inclusion Body Myositis

Liam G. Johnson, B Sci (Sp. Sci.) Hons.,*† Dylan J. Edwards, PhD,*† Susan Walters, B App Sci (Physio.),* Gary W. Thickbroom, PhD,* and Frank L. Mastaglia, MD*

Improvement in Aerobic Capacity After an Exercise Program in Sporadic Inclusion Body Myositis

Liam G. Johnson, BSc(Sp Sci)Hons,* Kelly E. Collier, BSc(Sp Sci)Hons,† Dylan J. Edwards, PhD,* Danielle L. Philippe,‡ Peter R. Eastwood, PhD,‡§¶ Susan E. Walters, BAppSci (Physio),* Gary W. Thickbroom, PhD,* and Frank L. Mastaglia, MD*

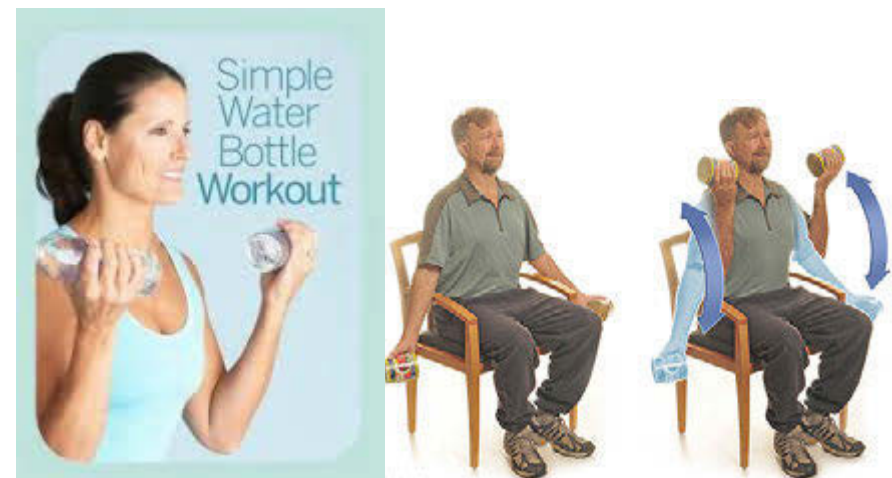
TABLE 2. Range of Exercises Prescribed and the Individualized Exercise Program Progression of Subject 5

Exercises	Preintervention	Postintervention
1. Whole body Sitting to standing (from standard height chair with arms)	3 sets of 6/day	3 sets of 10/day
2. Upper limbs Biceps curls* Shoulder presses* Seated rowing (Thera-Band) Wrist flexion/extension*	2 sets of 10/arm/day	2 sets of 10/arm/day
3. Lower limbs Calf raises (on tiptoe) Calf stretches (against wall) Vastus medialis (isometric) Ankle dorsiflexion		1 minute 2/day 15–20 seconds 3/day 2 sets of 20/day

*Holding a 375-g can of food in each hand.

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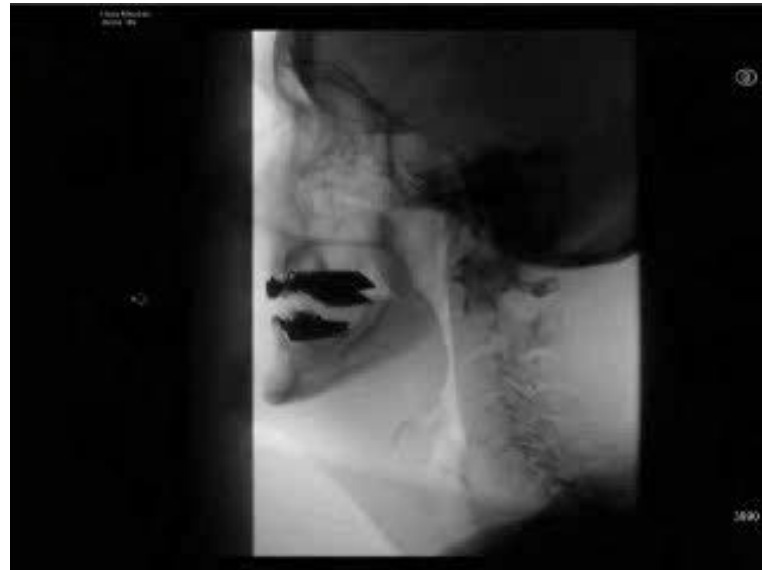
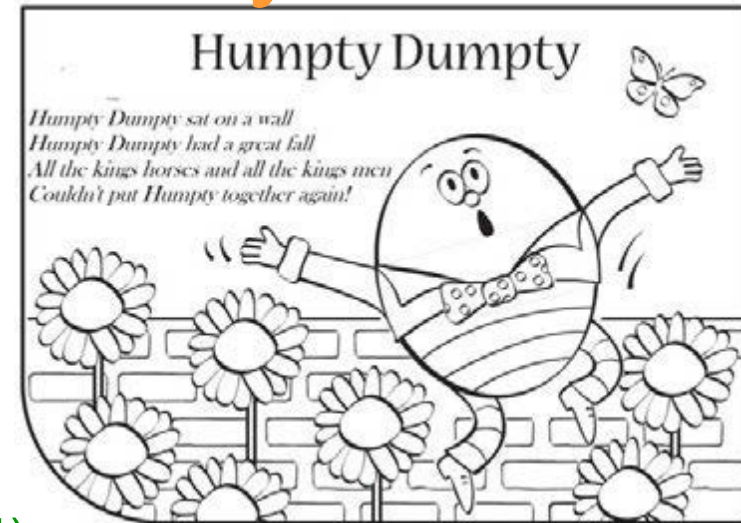


Now practical things

FOR DAY-TO-DAY

Practically day-to-day

- Bone health
 - DEXA
 - Vit D, Calcium
 - Bisphosphonates
- Swallowing (Oh, et al 2008; N = 24)
 - Cricopharyngeal myotomy
 - Balloon dilation
 - upper oesophageal
 - Botulinum toxin
 - PEG



To statin or not to statin?

- N= 14... 10 completed
- Simvastatin 40mg for 12 months
 - Pleiotropic actions:
 - Inhibition of inflammatory responses
 - Immunomodulatory effects
 - Improvement of endothelial function
 - Regulation of progenitor cells
 - Antioxidant...Neuroprotective properties
 - Muscle MRI, biopsy, oropharyngeal scintigraphy
 - No clinical improvement
- Safe
 - Myopathy < 0.2% (Ballantyne et al, 2003), rhabdomyolysis < 0.05% (Graham et al, 2004)
 - Statin-induced autoimmune myositis 1/ 100 000 (Mammen et al, 2011)

Pilot trial of simvastatin in the treatment of sporadic inclusion-body myositis

Cristina Sanerica • Marina Mora •
Enzo Ricci • Pietro Attilio Tonali •
Renato Mantegazza • Massimiliano Mirabella

Pain

- Some have significant pains
- Best Rx ???
 - NSAIDs
 - Tramadol

Issues in life

- “An embarrassment to my grandchildren”
 - Cannot keep up with partner
 - Being able to travel
-
- Tennis
 - Golf



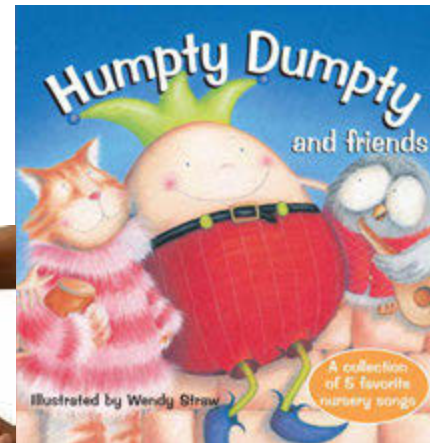
Checking for suicidal ideation...

- ...Something we can do?



The most valuable possessions

- Dictus bands
- Booster cushions
- VitalCall
- Shewee



Helping Hands



Thank you for your time

- And your attention
- And your patience
- And your teaching