

New research developments for IBM



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IBM: sporadic vs. „hereditary“ There is no true „hereditary IBM“

IBM



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Distal Myopathy
 E.g. Myofibrillar Myopathy



MDA, Internet

Classification of „hereditary IBM“ –outdated term!

- Old term: „Quadriceps-sparing IBM“ or „hereditary IBM“
 ⇒ International consensus: „GNE-Myopathy“
 (UDP-N-acetyl-glucosamine 2-epimerase/N-acetylmannosamine kinase)
- IBM-PFD: Mutation in VCP Gen
 (valosin containing protein; Paget disease and frontotemporal dementia)
- Myofibrillar myopathy (MFM): mutations in desmin, myotilin, titin etc.
- „IBM“ = „sIBM“

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Degeneration in Inflammation

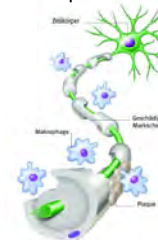
vs.

Inflammation in Degeneration

Neurologic Disorders

IBM

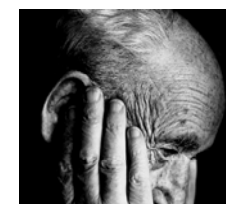
Multiple Sklerosis



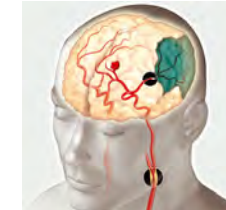
Parkinson's disease



Alzheimer's Dementia

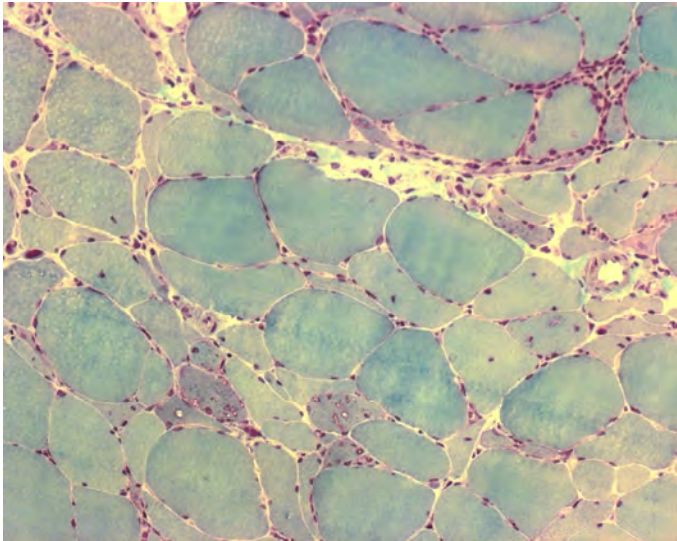


Stroke



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Muscle Pathology of Inclusion Body Myositis (IBM)



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Pathology of IBM

Acta Neuropathol (2015) 129:611–624
DOI 10.1007/s00401-015-1384-5

REVIEW

Amyloid deposits and inflammatory infiltrates in sporadic inclusion body myositis: the inflammatory egg comes before the degenerative chicken

Olivier Benveniste · Werner Stenzel ·
David Hilton-Jones · Marco Sandri · Olivier Boyer ·
Baziel G. M. van Engelen

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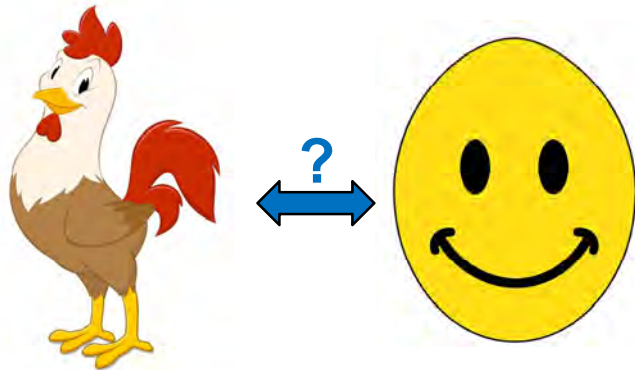
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REVIEW

Amyloid deposits and inflammatory infiltrates in sporadic inclusion body myositis: the inflammatory egg comes before the degenerative chicken

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1: Inflammatory mechanisms



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Explanation of icons

Studies in human

Blood samples



Muscle samples



Clinical study



Cell culture



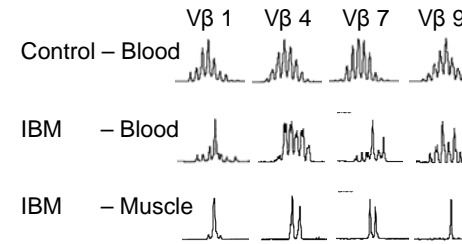
Mouse study



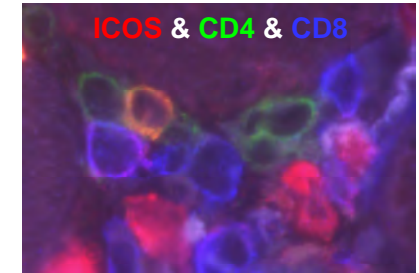
Specific Inflammation: T cells



Clonal T-cell expansion



T-cell attack of muscle fibers



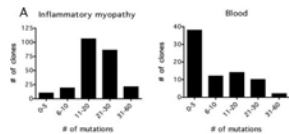
Salajegheh et al., Neurology 2007
Similar data: Dimitri et al., Brain 2006

Schmidt et al., Brain 2003
Similar data: Ikenaga et al., Neurology 2017

Specific Inflammation: B cells



Clonal B-cell expansion



Bradshaw et al., JI 2007
Greenberg et al., Neurology 2005

cN1A antibodies

Sera	No.	High Anti-Mup44 ⁺	
		No.	%
Total sIBM	94	31	33
DM	24	1	4
PM	22	1	5
Neuromuscular disorders	94	3	3
NHS ^c	32	0	0

Pluk et al., *Ann Neurol* 2013
Larman et al., *Ann Neurol* 2013

Additional data:
Lloyd et al., *Arthr Care Res* 2015
Herbert et al., *Ann Rheum Dis* 2015
Goyal et al., *JNNP* 2016
Lilleker et al., *Ann Rheum Dis* 2017

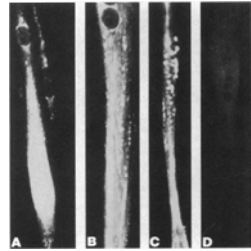
2: Degenerative mechanisms



β-amyloid accumulation in muscle cells



APP-CMV virus in human muscle cells: β-amyloid epitope



D= control

Askanas et al., PNAS 1996

β-amyloid/tau-HSV virus in C2C12 mouse muscle cells

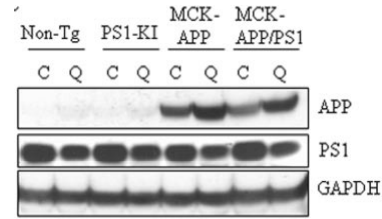


Christensen et al., JBC 2004

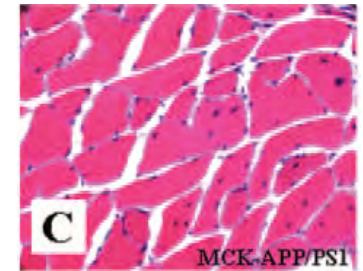
“Mouse-IBM”: APP-induced myopathy without inflammation



Double transgenic APP/PS-1 expression in skeletal muscle

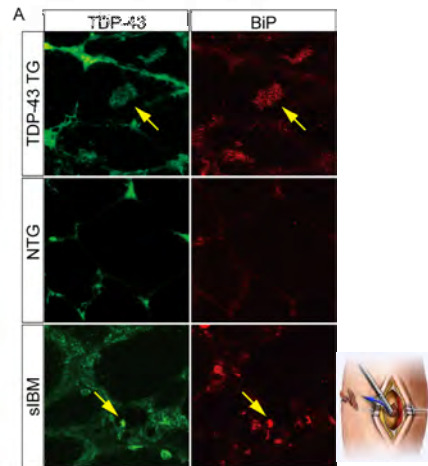
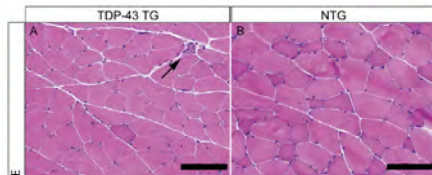
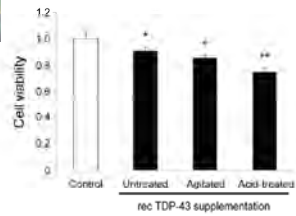


Myopathic histology



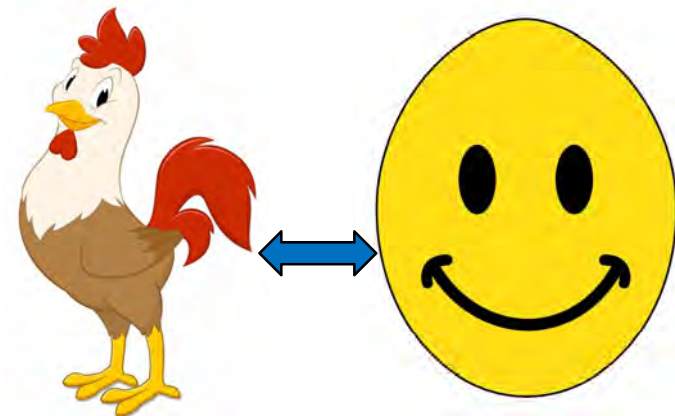
Kitazawa et al., AJP 2006

“Mouse-IBM 2”: TDP-43-induced myopathy without inflammation



Tawara et al., Exp. Neurol 2018

3: Interactions between inflammation & degeneration



Inflammation & degeneration: IL-1 β induces APP/ β -amyloid

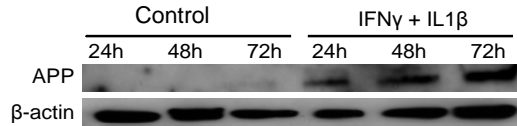
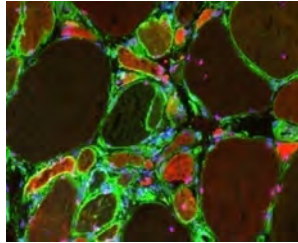


Biopsies



Cell culture

MHC-I β -amyloid DAPI



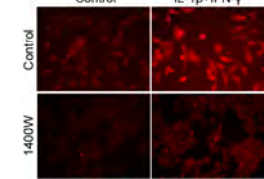
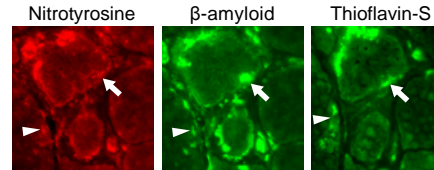
Interaction between NO-stress & β -amyloid ex vivo and in vitro



Biopsies



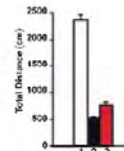
Cell culture: Nitrotyrosine



Chronic myositis upon overexpression of MHC-I in skeletal muscle



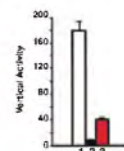
Healthy



9 months MHC-I on



5 months MHC-I on
4 months MHC-I off



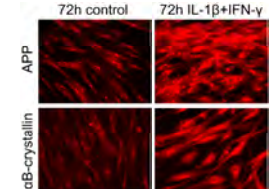
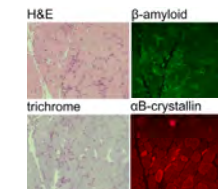
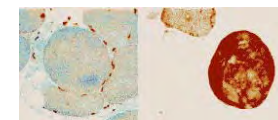
α B-crystallin in normal muscle fibers: „X-fibers“



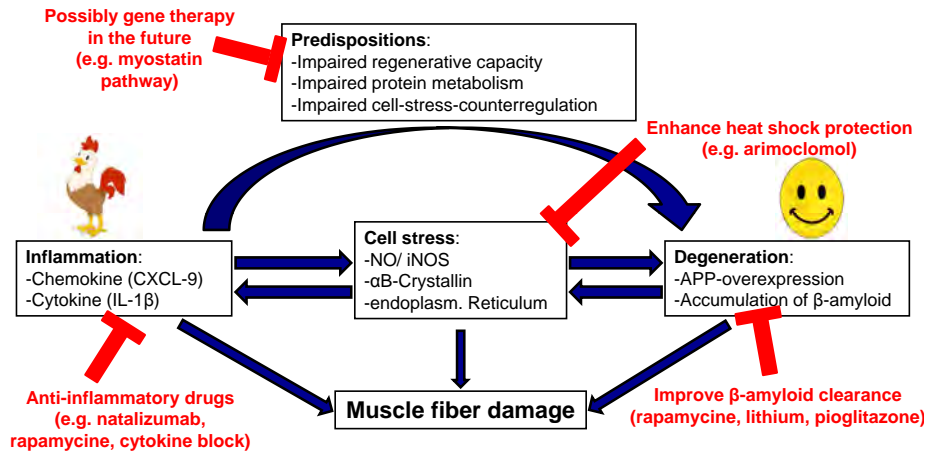
X-fibers in skeletal muscle



α B-crystallin and APP in muscle cells



Model of Pathogenesis of IBM and Treatment Strategies



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Schmidt, *Curr Op Rheum* 2017

Schmidt & Dalakas, *Exp Rev Clin Immunol* 2013

Previous clinical studies in IBM

- **Prednisolon:** Joffe MM et al. *Am J Med.* 1993; 94: 379-87.
- **Methotrexat:** Badrising UA et al. *Ann Neurol.* 2002;51:369-372.
- **Oxandrolon:** Rutkove SB et al. *Neurology.* 2002;58:1081-1087.
- **Cyclosporin A oder Tacrolimus:** Quartuccio et al. *Clin Exp Rheumatol.* 2007;25:246-251.
- **IVIG:** -Dalakas MC et al. *Neurology.* 1997;48:712-716.
-Walter MC et al. *J Neurol* 2000; 247: 22-28.
- **IVIG+Prednison:** Dalakas MC et al. *Neurology.* 2001;56:323-327.
- **IFN-β1a:** -Muscle Study Group. *Neurology.* 2001;57:1566-1570.
-Muscle Study Group. *Neurology.* 2004;63:718-720.
- **TNF-α block (etanercept):** Barohn et al. *Neurology.* 2006; 66 (S1): 123-4.
- **Anti T-lymphocyte-globulin:** Lindberg et al. *Neurology.* 2003; 61: 260-262.
- **Campath:** Dalakas et al. *Brain.* 2009; 132: 1536–1544.

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Recent clinical trials

- **Arimoclolomol:** phase 2 completed (24 pat.), phase 2/3 active (150 pat.)
- **Rapamycine:** (Autophagy/Immunsuppression): phase 2 study, 44 pat., completed
- **Natalizumab (VLA4-Block):** phase 1 study (6 patients, open label)
- **Pioglitazone (PPAR γ -agonist):** phase 1 (15 patients, open label), active
- **Bimagrumab (myostatin block):** phase 2/3 study, completed
- **Follistatin (myostatin block):** phase 1 (15 patients, open label), completed

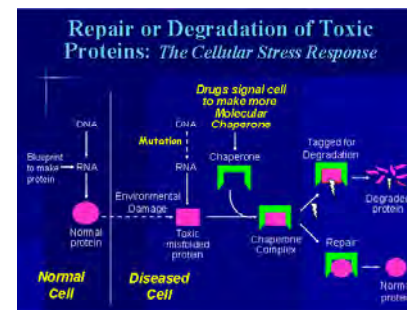
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www.clinicaltrials.gov

Heat shock proteins and arimoclolomol



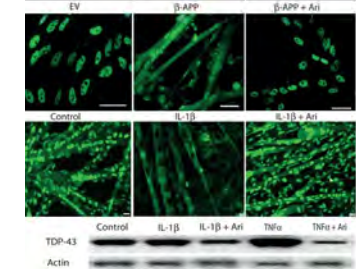
Improvement of ALS mouse model



Kieran et al., *Nat Med.* 2004, 10(4):402-5



Reduced protein accumulation in muscle cells



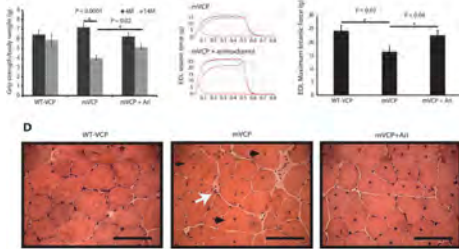
Ahmed et al., *Sci Translat Med*, 2016

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Proof-of-concept study with arimoclomol



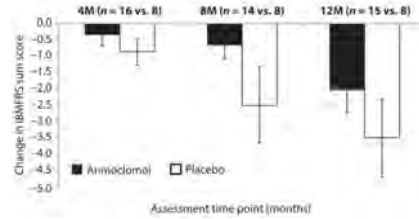
Improved strength and pathology in VCP-IBM mouse model



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Improved secondary endpoints in IBM (4 Mo. Therapy; n=2x12, double blind)



Ahmed et al., Sci Translat Med, 2016



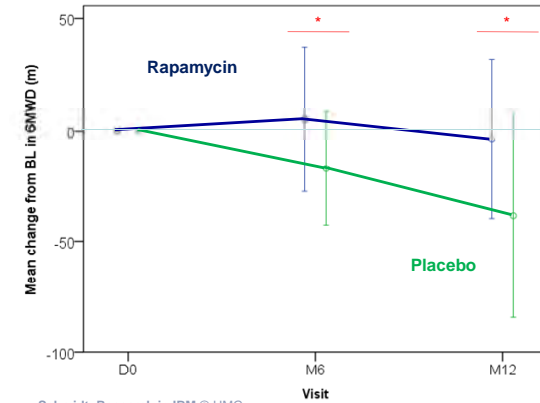
Sirolimus (rapamycin) in inclusion body myositis

Olivier Benveniste

- NCT02481453
- Randomized, double-blind, placebo-controlled, phase IIb study
- June 2015 and April 2017 in a single site (National Reference Center for Neuromuscular diseases of Paris, France).
- 22 patients under sirolimus (2 mg/d), 22 patients with placebo
- 52-week treatment period (Day 0 to Month 12).

Centre de Référence Maladies Neuro-Musculaires
Groupe Hospitalier Pitié-Salpêtrière, Paris

6MWD



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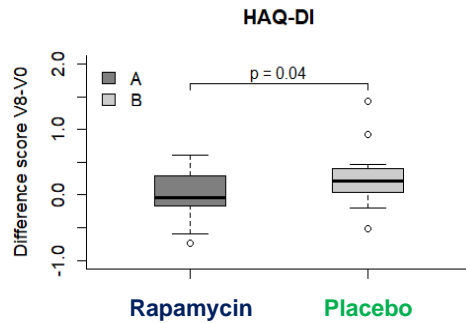


Sirolimus (rapamycin) in inclusion body myositis



HAQ

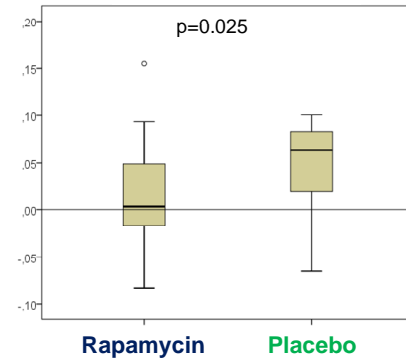
difference between baseline and M12



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Quantitative MRI

Rate of muscle replacement by fat (%): difference between baseline and M12
Quadriceps, left

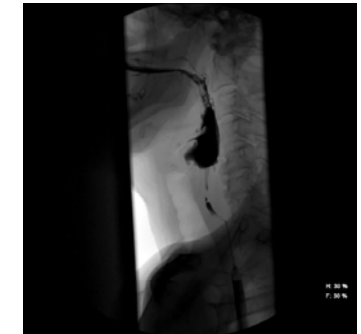


Dysphagia

Variety of swallowing



Videofluoroscopy: IBM with dysphagia



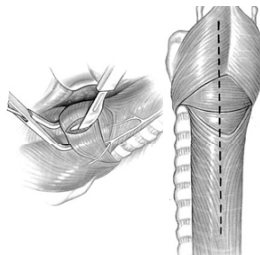
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Treatment of dysphagia in IBM

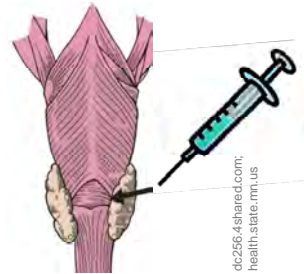
Ballon dilation



Myotomy



Injection of botulinumtoxin



Murata et al., Clin Med Insights Case Rep 2013

Sanei-Moghaddam et al., BMJ Case Rep. 2013

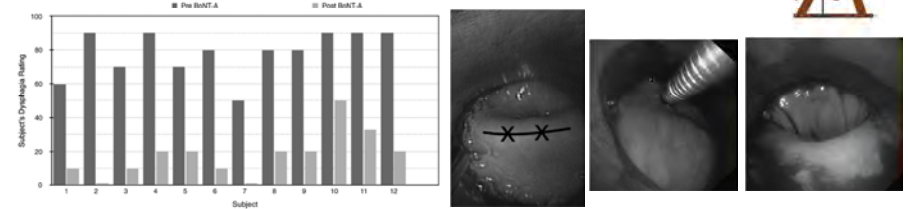
Liu et al., Can J Gastroenterol. 2004

Schmidt, *J Neuromusc. Disord* 2018
Schmidt, *Curr Op Rheumatol* 2017

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Botulinumtoxin for treatment of dysphagia in IBM

- Schrey et al., J Neurol Sci 2017: 12 v. 25 Pat. with dysphagia in IBM



- Di Pede et al., Neurol Sci 2016: 3 of 4 patients clearly improved up to 6 months

Table 1 Characteristics of subjects and response

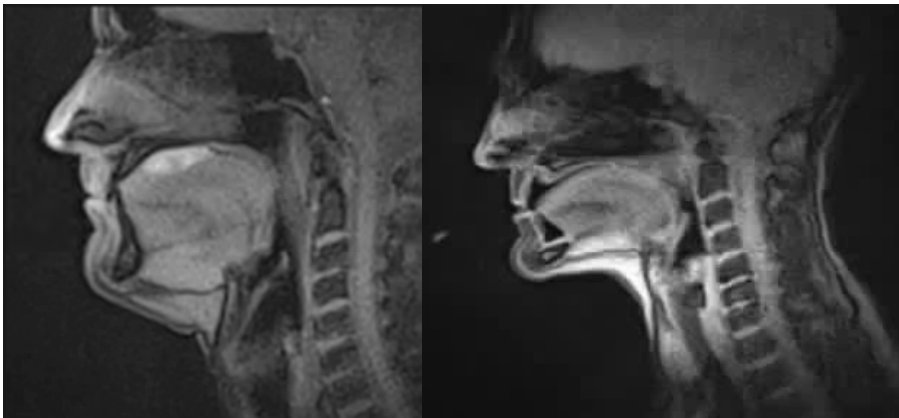
	Subject 1	Subject 2	Subject 3	Patient 4
Sex	Female	Female	Female	Male
Age at diagnosis of IBM (years)	73	74	72	82
Onset of dysphagia	At the time of IBM diagnosis.	Few months after IBM diagnosis	At the time of IBM diagnosis	At the time of IBM diagnosis
BoNT/A injection (dose)	8 UI BTX-A	30 UI BTX-A (other type)	8 UI BTX-A	8 UI BTX-A
PAS pre-post (at 1st rehabilitation cycle conclusion)	5/2	6/2	7/2	7/7
Duration of response (months)	6	6	14	—
Follow-up (years)	5	3	5	3

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Real-time MRI for assessment of swallowing

IBM without dysphagia

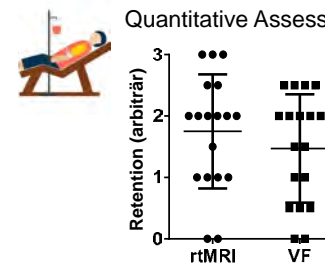
IBM with severe dysphagia



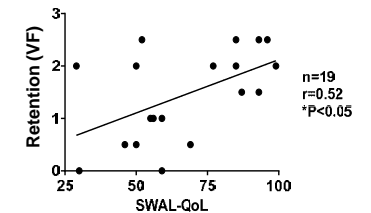
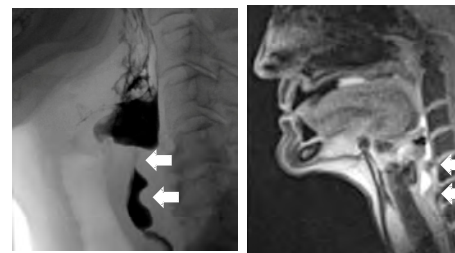
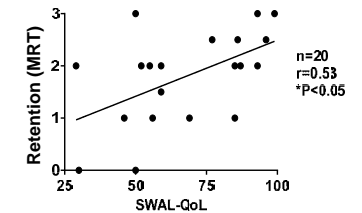
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Quantification of dysphagia in IBM by real-time MRI

Quantitative Assessment



Correlation with Swallowing Scale



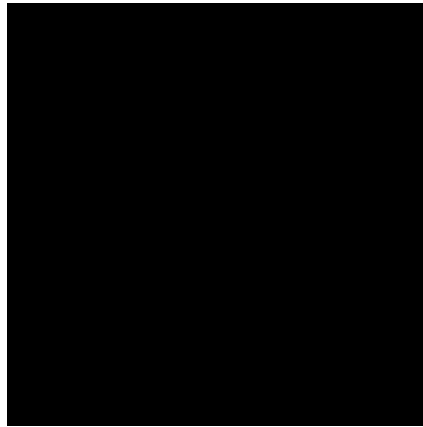
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Olthoff/ Schmidt et al., *Neurology* 2016

RT-MRT in IBM before / after botulinumtoxin

Before botulinumtoxin

After botulinumtoxin



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Patient Self-support Group for Myositis: Diagnosegruppe Myositis with the DGM

MYOSITIS NETZ



Established: June 2015

<http://www.myositis-netz.de/>



Von links nach rechts:
Silke Schlüter (Vorsitzende)
Klaus Jürgen Tack (stellvertretender Vorsitzender)
Michael Jehne (Delegierter)
Josef Dumm (stellvertretender Delegierter)

www.dgm.org/diagnosegruppe/myositis



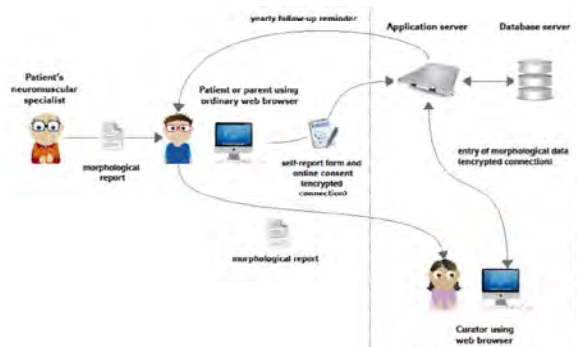
Workshop: March 2016 in Göttingen

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IBM Patient registry



Since February 2016 online (so far only for Germany):
www.ibm-register.de



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Recent review on myositis: open access Journal of Neuromuscular Disorders

Journal of Neuromuscular Diseases 5 (2018) 109–129
DOI 10.3233/JND-180308
IOS Press

Review

Current Classification and Management of Inflammatory Myopathies

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Thank you for your attention!

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