New research developments for IBM

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

IBM
Distal Myopathy
E.g. Myofibrillar Myopathy

Classification of „hereditary IBM“ – outdated term!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“
Pathology of IBM

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

Olivier Benveniste, Werner Stemmer, David Hilton Jones, Marco Sandri, Olivier Boyer, Briel G. M. van Engelen

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1: Inflammatory mechanisms
**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
  - Control – Blood
  - IBM – Blood
  - IBM – Muscle
  - Similar data: Salajegheh et al., Neurology 2007
  - Similar data: Dimitri et al., Brain 2006

**Specific Inflammation: B cells**
- Clonal B-cell expansion
- cN1A antibodies

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- 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., JNMP 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

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

Askanas et al., PNAS 1996

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

Interactions between inflammation & degeneration

Tawara et al., Exp. Neurol 2018

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

Biopsies

MHC-I β-amyloid DAPI

Cell culture

Control IFNγ + IL1β

APP 24h 48h 72h

β-actin

24h 48h 72h

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

Biopsies

Nitrotyrosine β-amyloid Thioflavin-S

Cell culture: Nitrotyrosine

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

αB-crystallin in normal muscle fibers: „X-fibers”

X-fibers in skeletal muscle

αB-crystallin and APP in muscle cells

Banwell & Engel, Neurology 2000

Muth et al., JNNP 2009

Kannanbujhala Nagaaraju*, Nina Raben*, Ilka Leewildt*, Tommaso Parker*, Paul J. Rochon*, Eunice Lee*, Carol Dannig*, Ryusuke Wada†, Cynthia Thompson†, Giel Bahtijar†, Joseph Craft†, Fabio Houtt van Heukelom*, and Paul Peitz‡

PNAS | August 1, 2000 | vol. 97 | no. 16 | 9209-9214
Model of Pathogenesis of IBM and Treatment Strategies

**Predispositions:**
- Impaired regenerative capacity
- Impaired protein metabolism
- Impaired cell-stress-counterregulation

**Inflammation:**
- Chemokine (CXCL-9)
- Cytokine (IL-1β)

**Cell stress:**
- NO/iNOS
- αB-Crystallin
- Endoplasm Reticulum

**Degeneration:**
- APP-overexpression
- Accumulation of β-amyloid

**Muscle fiber damage**

**Anti-inflammatory drugs**
- (e.g. natalizumab, rapamycin, cytokine block)

**Heat shock protection**
- (e.g. arimoclomol)

**Improve β-amyloid clearance**
- (rapamycin, lithium, pioglitazone)

**Recent clinical trials**
- Arimoclomol: phase 2 completed (24 pat.), phase 2/3 active (150 pat.)
- Rapamycin: (Autophagy/Immunosuppression): phase 2 study, 44 pat., completed
- Natalizumab (VLA4-Block): phase 1 study (6 patients, open label)
- Pioglitazone (PPARγ-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

**Heat shock proteins and arimoclomol**
- Improvement of ALS mouse model
- Reduced protein accumulation in muscle cells

**Previous clinical studies in IBM**
Proof-of-concept study with arimoclomol

Improved strength and pathology in VCP-IBM mouse model

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


Sirolimus (rapamycin) in inclusion body myositis

- NCT02481453
- Randomized, double-blind, placebo-controlled, phase Ib 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)

6MWD

Dysphagia

Variety of swallowing

Quantitative MRI

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

Quadriceps, left

p=0.025

Rapamycin

Placebo

Schmidt: Research in IBM © UMG

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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

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

Schmidt: Research in IBM © UMG

Real-time MRI for assessment of swallowing

IBM without dysphagia    IBM with severe dysphagia

Olthoff/ Schmidt et al., Neurology 2016

Quantification of dysphagia in IBM by real-time MRI

Quantitative Assessment

Correlation with Swallowing Scale

Olthoff/ Schmidt et al., Neurology 2016
RT-MRT in IBM before / after botulinumtoxin

Before botulinumtoxin

After botulinumtoxin

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

Established: June 2015

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

Workshop: March 2016 in Göttingen

IBM Patient registry

Since February 2016 online (so far only for Germany):

www.ibm-register.de

Recent review on myositis: open access
Journal of Neuromuscular Disorders

Current Classification and Management of Inflammatory Myopathies

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Thank you for your attention!

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