3rd Congress of the European Academy of Neurology

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Teaching Course 18

How to diagnose a muscle disorder - Level 1

Muscle imaging

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Volker Straub

Disclosure statement

- I am or have been a principal investigator for trials sponsored by Sanofi Genzyme, GSK, Prosensa/BioMarin Pharmaceuticals, Ionis Pharmaceuticals, and Sarepta Therapeutics
- I received speaker honoraria from Sanofi Genzyme
- For the last 3 years I am or have been on advisory boards for Audentes Therapeutics, Biogen, Bristol-Myer Squibb, Exonics Therapeutics, Italfarmaco S.p.A., Sarepta Therapeutics, Summit Therapeutics, Tivorsan Pharmaceuticals, TrophyNOD, and Wave Therapeutics
- For the last 3 years I have or had research collaborations with Ultragenyx and Sanofi Genzyme

Newcastle Muscle MRI as a diagnostic tool for genetic muscle diseases

How to diagnose a muscle disorder - Level 1
Pattern recognition – the quiz
>1000 variants in 5 of 170 candidate genes – in 500 patients

<table>
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<tr>
<th>GENE</th>
<th>mRNA (bp)</th>
<th>EXONS</th>
<th>dbSNPs</th>
<th>MYO-SEQ variants (&lt;1%)</th>
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ColVI  RYR1  TTN
diagnostic procedures in muscle diseases

- clinical history
- clinical examination
- investigations
  - blood tests
  - electrophysiology
  - cardiac function
  - lung function
  - imaging
  - muscle biopsy
  - protein analysis
  - genetic analysis
    ➔ confirmed diagnosis
Frontal or coronal plane divides the body or an organ into front (anterior) and back (posterior) portions.

Transverse (cross-sectional), axial or horizontal plane divides the body or an organ into upper (superior) or lower (inferior) portions.

**1.5 vs 3-tesla MRI**

A high field strength provides a better signal to noise ratio.

At the same resolution, images on a higher field strength magnet can be acquired faster.
what's the indication for a muscle MRI?

51 y. of age
15 y. history of weakness
CK 680 U/l

43 y. of age
6 y. history of weakness
CK 840 U/l

Bethlem myopathy
Pompe disease
which diseases might a muscle MRI help to diagnose?

- Muscular Dystrophies
- Myofibrillar Myopathies
- (congenital) Myopathies

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<th>LGMD1</th>
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1 = autosomal dominant
2 = autosomal recessive
90% LGMD2 (CK↑↑↑)
10% LGMD1 (CK n -)
Clinically, Duchenne/Becker muscular dystrophy is the most common form of LGMD!

⇒ each male with limb girdle weakness should first be considered to have a dystrophinopathy

Always assume that a female with limb girdle weakness and elevated serum CK levels could be a manifesting DMD/BMD carrier!
Asymmetry is a typical feature.
29 y old female, CK 2.500 U/l, limb girdle weakness

LGMD2A
Typically involvement of the hamstring and the medial gastrocnemius and soleus muscles

LGMD2A
CAPN3 gene mutation: c643-663del & c1256A>G

FVC: 5.94 litres, 147%; CK: 4300 U/l
From „Neuromuscular Imaging”, M.P. Wattjes, Department of Radiology, Amsterdam, NL; D. Fischer, Department of Neuropaediatrics, Basel, SL (Eds.)
Calpainopathies - Conclusion

- LGMD2A predominantly involves the posterior thigh muscles
- During the course of the disease, the anterior compartment becomes equally affected
- In contrast to severe MRI changes, some patients are able to walk well into their 40ies

The Jain COS Consortium

- 182 DYSF patients with baseline muscle MRI

<table>
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</table>
Muscle Involvement - MRI T1W

Whole body

0 - normal appearance
1 - mild involvement
2 - moderate involvement
4 - end stage

- 182 patients - baseline MRI
- 84 whole body MRI
- 98 lower limbs only
46 y old male, high CK, limb girdle weakness

Sparing of the lower leg muscles in a patient with limb girdle muscular dystrophy:

Think of the sarcoglycanopathies (LGMD2C-F) or Pompe disease!
LGMD2C-F - Sarcoglycanopathies

- variable disease onset
- proximal muscle weakness
- Serum-CK ↑↑
- respiratory and cardiac involvement

LGMD2D
SGCA gene mutation: c371C>T & c739G>A

Heart: normal function
FVC: 2.77 litres, 59%
LGMD2E
SGCB gene mutation: IVS2+5G>A

Heart: fractional shortening of 27%, evidence of reduced intra-ventricular septal motion
FVC: 2.12 litres, 41%

courtesy of Giorgio Tasca

LGMD2C-2F

courtesy of Giorgio Tasca
Differential diagnosis: Dystrophinopathies

sarcoglycanopathy

BMD

courtesy of Giorgio Tasca

Differential diagnosis: LGMD2I

sarcoglycanopathy

FKRP

courtesy of Giorgio Tasca
Viking Founder Mutations in the UK:

- LGMD2I
- LGMD2L
- calpainopathy


LGMD2I FKRP gene mutation: Homozygous c826C>A
LGMD2I – assessment of muscle pathology by MRI

Selective pattern of involvement

LGMD2L – anoctamin5

proximal weakness of lower limbs + high CK!
LGMD2L – anoctamin5

Sarkozy A. et al., Neuromuscul Disord 2012

No weakness, mild calf hypotrophy, mild myopathic changes on Bx (deltoid)
Schematic representation of muscle involvement. **Red**: most severely affected muscles; **green**: least affected muscles

A *POGLUT1* mutation causes a muscular dystrophy with reduced Notch signaling and satellite cell loss

E Servián-Morilla et al., EMBO Mol Med 2016
Bethlem Myopathy

Collagen VI-related disorder

Mercuri et al., Ann Neurol 2010
Myofibrillar Myopathies
(desminopathies, protein surplus myopathies)

Desmin
Myotilin
ZASP
αB-Crystallin
Filamin C
BAG3
DNAJB6
Titin
VCP
Myofibrillar myopathies

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<th>MUSCLES</th>
<th>DES</th>
<th>MYOT</th>
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<tr>
<td>Soleus</td>
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<tr>
<td>Semitendinosus</td>
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<td>Semimembranosus</td>
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<td>Gracilis</td>
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<tr>
<td>Vasti intermedius/medialis</td>
<td>1/9</td>
<td>7/11</td>
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</table>

 Straub et al., Neuromuscul Disord 2012
Desmin associated myopathy

The most affected muscles are:
Thigh: the semitendinosus, sartorius and gracilis muscles
Calf: the extensor digitorum longus muscles

Myotilin associated myopathy

The most affected muscles are:
Thigh: the adductor magnus and semimembranosus muscles
Calf: the soleus, medial gastrocnemius and tibialis anterior muscles
Titin associated myopathy

62 year old male

40 year old male

51 year old female with an axial, non-progressive myopathy
RYR1-associated myopathies

MTM1, manifesting carrier

SEPN1 associated myopathy (RSS)
SEPN1 associated myopathy (RSS)

Myopathy
SEPN1

Muscle imaging findings in GNE-myopathy

G. Tasca et al., J Neurol (2012)
Muscle imaging findings in GNE-myopathy

Muscles prominently and invariably involved from the early stages of GNE myopathy include:
- the gluteus minimus (a red)
- the biceps femoris short head (b green)
- the tibialis anterior (c blue)
- the extensor hallucis/digitorum longus (c yellow)
- the soleus (c violet)
- the gastrocnemius medialis (c orange)

The femoral quadriceps muscle is normally well preserved.

Pattern recognition – the quiz
Save the Date!

November 19-21, 2017 | Berlin, Germany
Imaging in Neuromuscular Disease 2017
First International Conference on Imaging in Neuromuscular Disease

The conference programme will feature internationally recognized invited speakers highlighting developments and advances in all aspects of muscle imaging with sessions which will include:

Diagnostic Muscle Imaging - New Imaging Techniques - Quantitative Muscle Imaging

Young researchers and trainees are encouraged to attend and participate. Selected abstracts will be featured for platform presentation during the sessions and all posters are eligible for poster awards. Further programme information and how to register for this conference can be found at conference.myo-mri.eu

Thank you

Special thanks to Jordi Díaz Manera, Giorgio Tasca and Maggie Walter