The Muscle Biopsy.

From essential Diagnostic tool to still an important Procedure?

Svalbard 3-5 Sept. 2019

Sigurd Lindal
Mayo Clinic was a role model

The needs of the patient comes first
The surgical procedure of muscle biopsy

- "Open" muscle biopsy
- Processing of muscle tissue
  - Should start immediately after surgery
  - To obtain optimal tissue quality, correct handling of the muscle specimen is essential
  - A technologist should be present in the operating room
- Divided into 3 specimens
  - For cryostat sections
  - Electronmicroscopy
  - Formalin

Rest: Frozen For genetic /Biobank
Muscle biopsy – staining for light microscopy
First human Musle Biopsy
Griesinger & Bilrot 1865

The biopsy was taken in Zurich, Switzerland on the 15. of August 1864

*Open muscle biopsy, under chloroform anesthesia from the deltoid muscle of a 13 year old boy*

”Muscle tissue with necrosis and pseudohypertrophy”, today known as Duchennes Muscular Dystrophy
Which structural features do we observe in the microscope?

1. Myopathic Changes
2. Neurogenic Changes
3. Inflammatory Changes *
   Immune mediated myopathies

Groups with atrophic fibers surrounded by hypertrophic fibres
1- Muscle biopsy in Myopathy

Myopathic Changes

- Myofiber necrosis
- Myophagocytosis
- Regeneration
- Oedema (swelling)
- Myopathic rounded and atrophic fibres
- Increase of internal nuclei
- Myofiber Hypertrophy-splitting
- Endo/perimysial fibrosis
- Nuclear chains
- Moth-eaten fibers
- Ring fibers
- Whorled fibers
- Vacuoles
- Inclusions
- Inflammation*
2 – Neurogenic disorders have the following characteristic in muscle biopsy:

- Angulated atrophic myofiber (NADH+)
- Fiber-type grouping
- Group atrophy
- Target fibers
- Nuclear clumps
Fiber type grouping & Reinervation (ATPase 4.5) Targets (NADH)
Important groups that can be diagnosed by muscle biopsy

- Muscular dystrophies
- Congenital Myopathies
- Inflammatory Myopathies
- Metabolic myopathies
  - Mitochondrial myopathies
  - Glycogen storage diseases
- Neurogenic Disorders
Immunohistochemical staining (dystrophin)
Western Blot
Congenital Myopathies

- Central Core Disease
- Nemaline Myopathy
- Myotubular Myopathy
- Centronuclear Myopathy
- Congenital fibre type disproportion
Congenital Myopathies

- Central Core Disease
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- Myotubular Myopathy
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Electron Microscopy (EM) – in Tromsø....
Ragged-Red-Fibres (RRF) and EM-findings in Mitochondrial Myopathy
PAS STAIN
(Pompes)

EM: accumulation of Lysosomal glycogen
Polymyositis - autoinvasion
Inclusion Body Myositis -IBM
Interdisciplinary meetings...
Diagnosis of Neuromuscular Disorders

3 Pillars

1. **Clinical** (Neurology, Neurophysiology, Pediatric and Rheumatology)
   - Decides to take the muscle biopsy- (analysis -CK, clinical ex.
   - Electromyography (EMG)
   - Imaging

2. **Muscle biopsy** (Dept. of Pathology in Norway)
   - Decrease in number

3. **Medical Genetic Tests** (NGS) Increased number

• **IS MUSCLE BIOPSY NECESSARY?**
Biopsier samlet med andel konsultasjoner

- 2000: 113
- 2004: 110
- 2008: 133
- 2012: 95
- 2014: 70
- 2018: 45

Konsultasjoner:
- 2000: 20
- 2004: 29
- 2008: 30
- 2012: 29
- 2014: 29
- 2018: 1

Legende:
- Biopsier samlet
- Konsultasjoner
Next Generation Sequencing (NGS)
Allows the sequencing of hundreds of genes from hundreds of patients, simultaneously.

Department of Medical Genetics, UNN
Muscle biopsy pathology or a shift to "liquid muscle pathology"

Editorial Curr Opin Neurology B.Schoser 2016

- Muscle pathology (BIOPSY) has been the diagnostic corner-stone of more than 800 distinct muscle disorders over the last 5 decades
- Nevertheless, several classical clinical indication and reliable genetic testing, have made the muscle biopsy redundant;
- Next-generation sequencing techniques - NGS (gen panel), has supplanted muscle pathology for making the correct diagnosis (much cheaper and more reliable)
Only Acquired myopathies: Biopsy in first line
Dominant myopathies: Direct gene analysis
Recessive Myopathies: Focused gene panel/exome/genome analysis
Muscle biopsy and the future?
B Schosser

**Conclusion:** Next-generation sequencing (NGS) and the clinical exome/genome approach combined with proteomics, are now taking priority in the diagnostics setting of a "modern liquid muscle pathology"

Muscle biopsy has still an important role and the analytical scientific and medical expertise in muscle pathology is needed for a full understanding of the *pathogenesis* and future *therapies*
169 pediatric patients (<18year)
-Neuromuscular related symptoms
-Neurologist were referring physician (89%)
Rest from Rheumatology and Medical Genetics
-Left m. vastus lateralis (82%)

**Structural changes** (3 categories)

1 Normal pathology n=45 (27%)
2-Minimal changes n=23 (14%)
not sufficient for a definitive diagnosis.
3 Pathological changes n=101 (60%)
sufficient to make pathologic diagnosis (based on description)

**Results:**

In 101 patients (60%) the pathologists were successful in reaching a pathological diagnosis.

- Type 2 fiber atrophy (n=16)
- Type 1 fiber atrophy (n=13)
- Denervation pattern (n=11)
Conclusion:

We find that muscle biopsy is *consistently useful* in helping pediatric patients with a final diagnosis.

*In this matter, we disagree with most of the reported literature about the diagnostic yield of muscle biopsy.*

**Muscle biopsy**

(Immunohistochemistry, Western blot, EM, fibroblast culture, biochemistry – respiratory chain analysis)

Combined

with NGS (genetics)
Have a wonderful seminar on Svalbard!