Histopathological Features of Pompe Disease

Dr. Ronnie S.L. Ho

MBBS (HK), FHKCPath, FHKAM, FRCPC (Anatomical Pathology)

Consultant Pathologist

Gleneagles Hospital Hong Kong

MAT-HK-2300782-1.0-10/2023

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Disclosure

I have nothing to disclose

Clinical Phenotypes of Type II GSD / Pompe disease

Infantile (Pompe disease – most severe)

Late-onset including adult

Glycogen accumulation

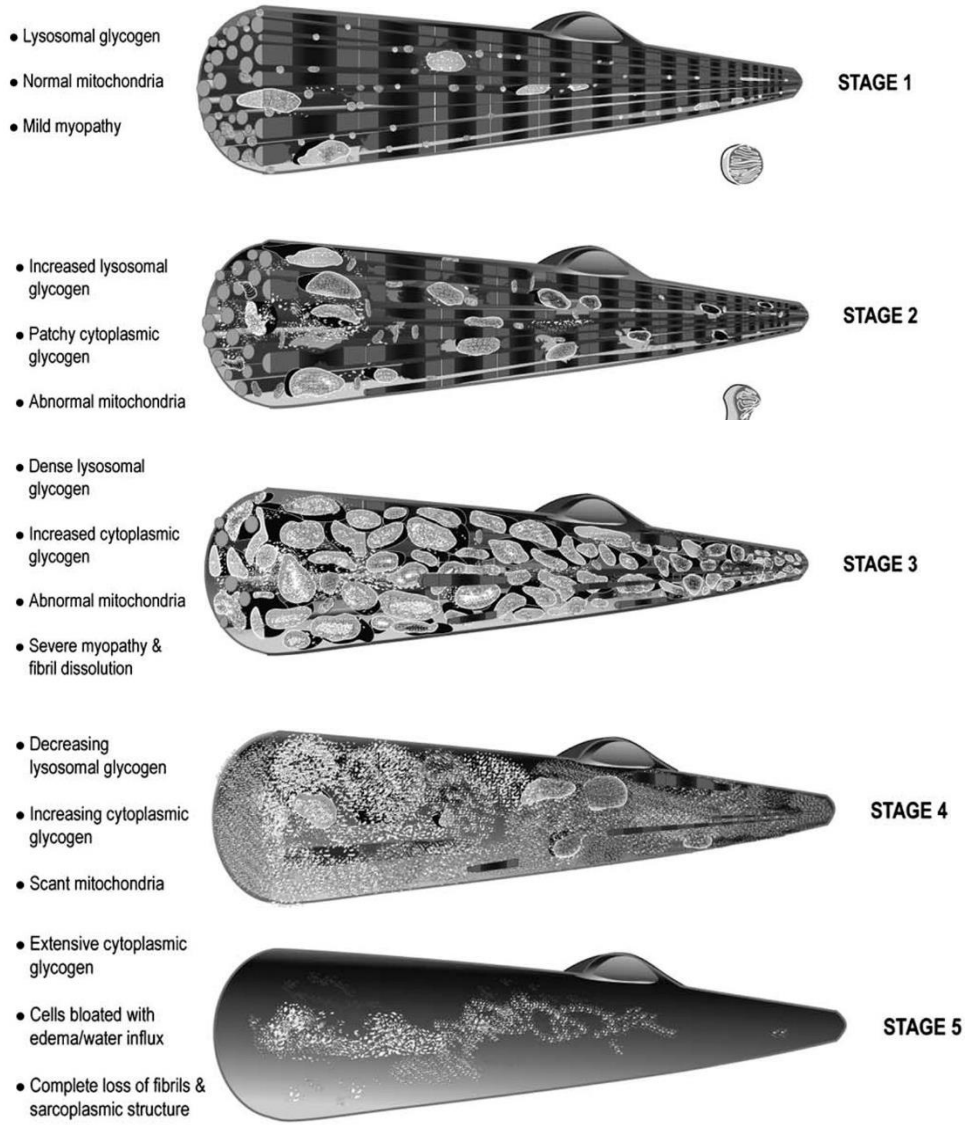
Generalised disease, including
- Skeletal muscle (including tongue)
- Heart
- Central nervous system

Understanding the skeletal muscle pathology (I)

Deficiency of **lysosomal** enzyme acid α-glucosidase (GAA)

Progressively enlarged glycogen-filled lysosomes & eventual rupture

Release of glycogen & lytic enzymes into sarcoplasm; extralysosomal glycogen accumulation; destroys contractile elements; water influx



Thurberg et al. Lab Invest. 2006 Dec;86(12):1208-20.

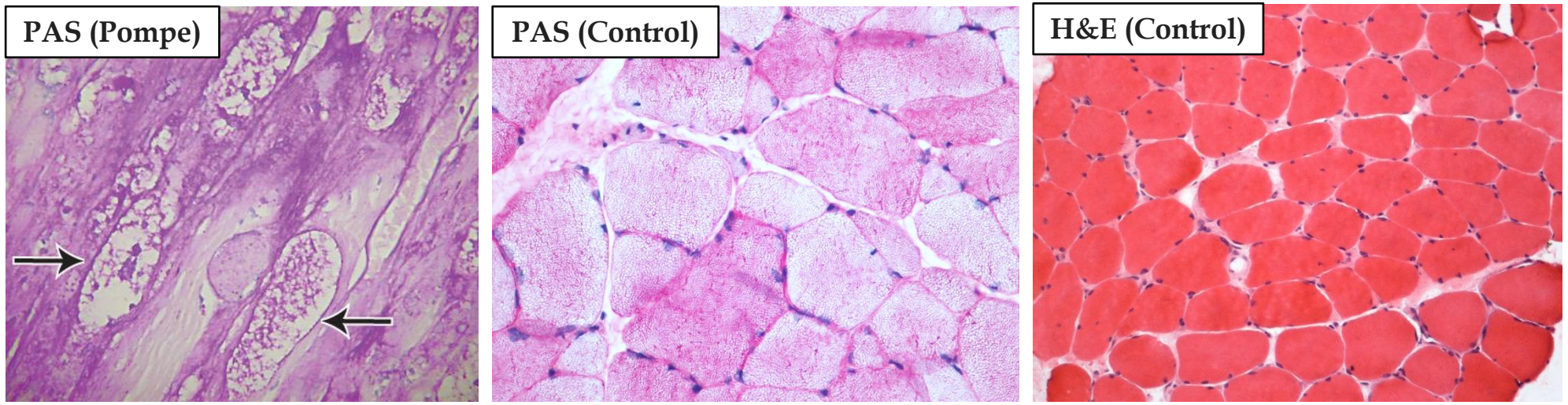
Classical biopsy findings in Pompe disease

Marked **vacuolar** appearance of many fibres with loss of myofibrils

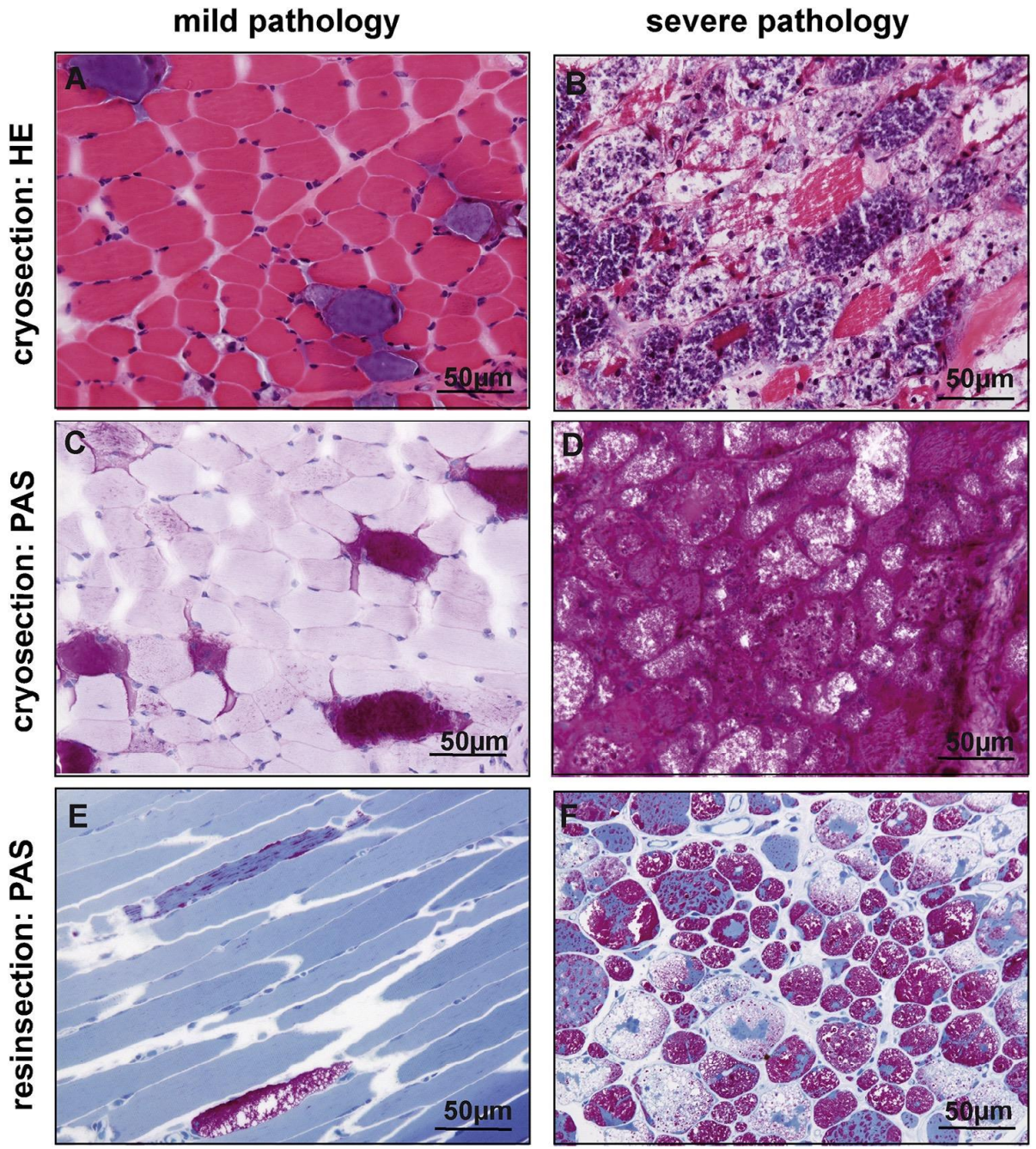
Abundant glycogen deposits

- Positive with **periodic acid-Schiff (PAS) stain**, at least partially digested by **diastase (D)**
- Can be lost in routine tissue processing
  - *PAS staining of resin sections can be helpful*

Vacuoles may or may not contain glycogen



Principles of Rubin's Pathology, 7e, 2019



Schänzer et al. Neuromuscul Disord. 2017 Feb;27(2):141-152.

Glycogen accumulation

Not always readily demonstrable in muscle biopsies of especially adult patients

If it were the sole mechanism, response to enzyme replacement (in skeletal muscle) should have been better.

Something abnormal was described (in adult-onset patients) in 1970 but neglected in later studies until 2008.

Engel AG. Brain (1970) 93:599–616.

Nascimbeni AC et al. Neurology (2008) 70:617–626.

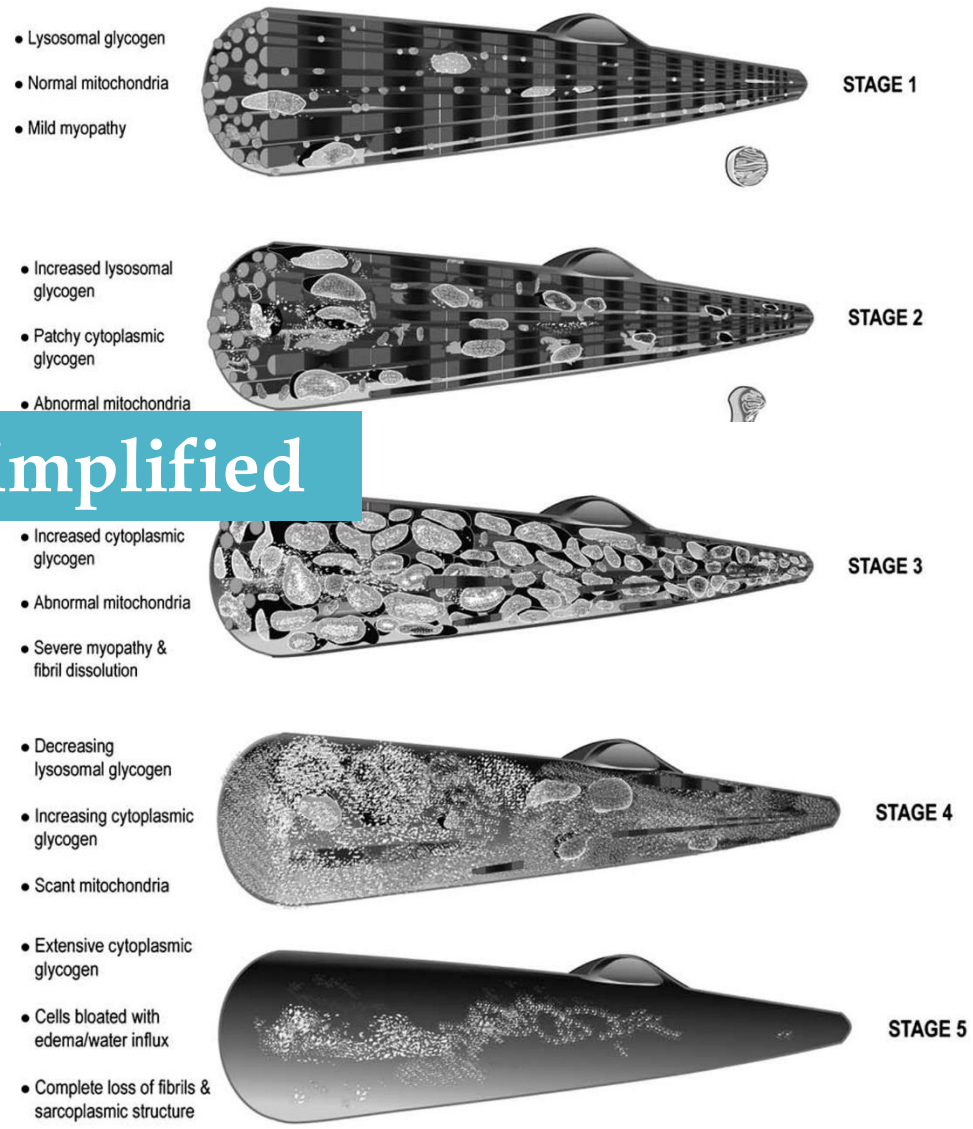
Understanding the skeletal muscle pathology (I)

Deficiency of **lysosomal** enzyme acid α-glucosidase (GAA)

Progressively enlarged glycogen-filled lysosomes & eventual rupture

Release of glycogen & lytic enzymes into sarcoplasm; extralysosomal glycogen accumulation; destroys contractile elements; water influx

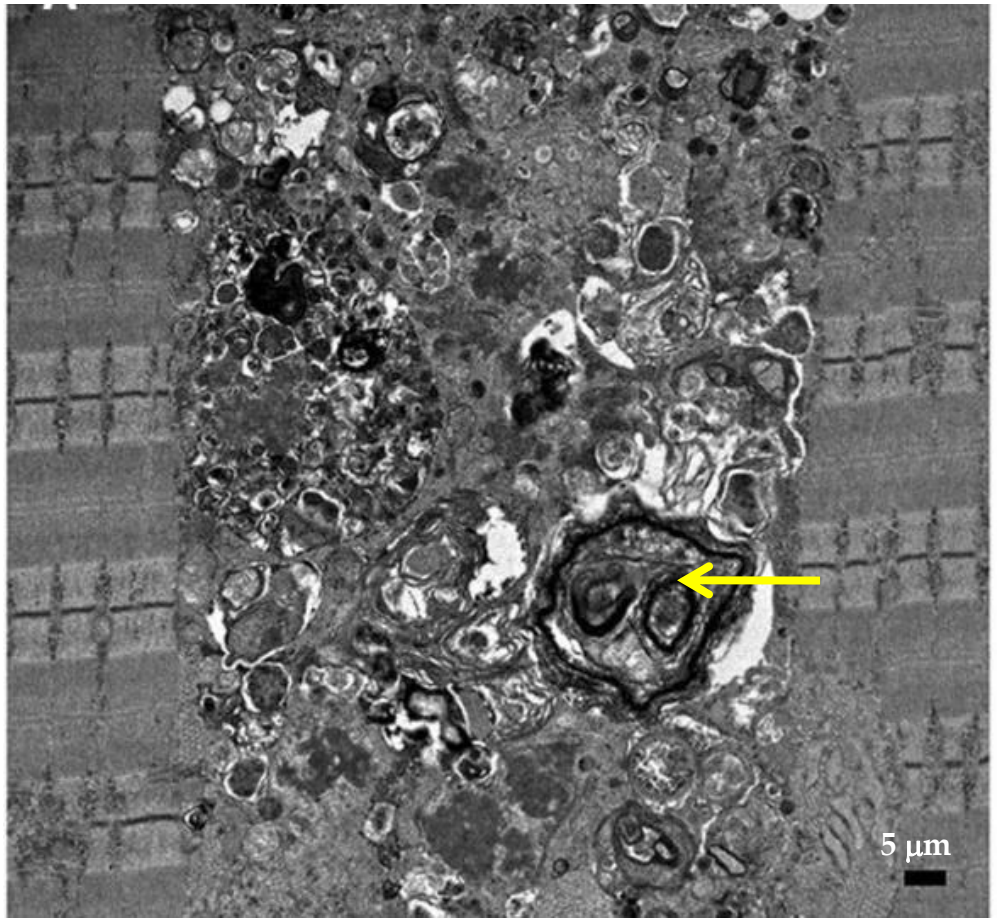
Oversimplified



Thurberg et al. Lab Invest. 2006 Dec;86(12):1208-20.

Understanding the skeletal muscle pathology (II)

Role of autophagy



Failure of glycogen digestion results in local starvation stimulating autophagy

↓

Defective fusion of lysosomes and autophagosomes, leading to **autophagy build-up**

↓

Numerous autophagosomes, clustered late endosomes and lysosomes with broken borders, and autofluorescent material, cellular debris, undigested autophagic substrates, such as p62/SQSTM1 and potentially toxic ubiquitinated protein aggregates

Autophagic myopathy

Lim et al. Front Aging Neurosci. 2014 Jul 23;6:177.

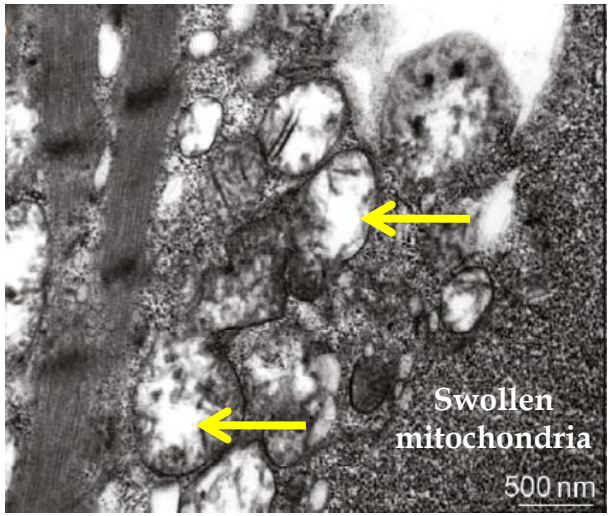
Understanding the skeletal muscle pathology (III)

Impaired autophagy affects **mitophagy** and causes **mitochondrial abnormalities** & Ca^{2+} overload, increased **reactive oxygen species**, accelerated deposition of **lipofuscin**

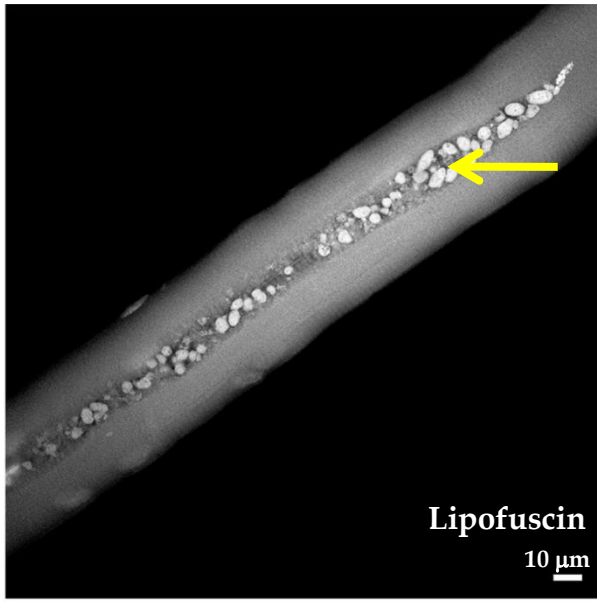
Lipofuscin further reduces lysosomal degradative capacity & autophagic turn-over

Glycogen-laden lysosomes, lakes of cytoplasmic glycogen, autophagic debris, lipofuscin

Large clusters of noncontractile material impairs contractility and leads to muscle damage



Kulessa et al. Neuropathol Appl Neurobiol (2020), 46, 359–374

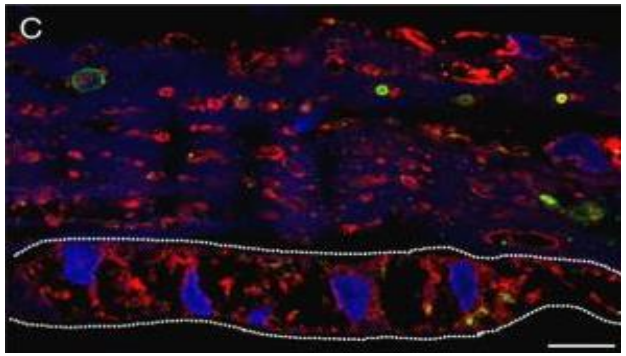


Lim et al. Front Aging Neurosci. 2014 Jul 23;6:177.

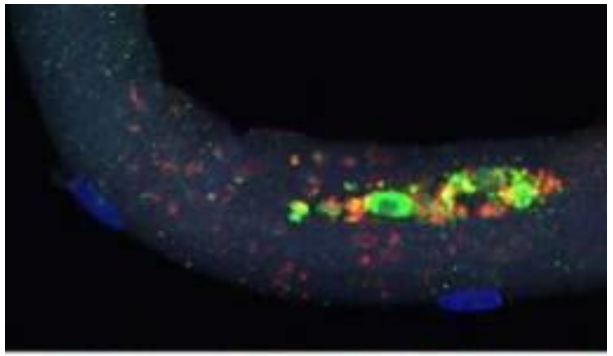
Understanding the skeletal muscle pathology (IV)

Raben N et al. **Differences in the predominance of lysosomal and autophagic pathologies between infants and adults with Pompe disease: implications for therapy**. Mol Genet Metab. 2010 Dec;101(4):324-31.

Infant

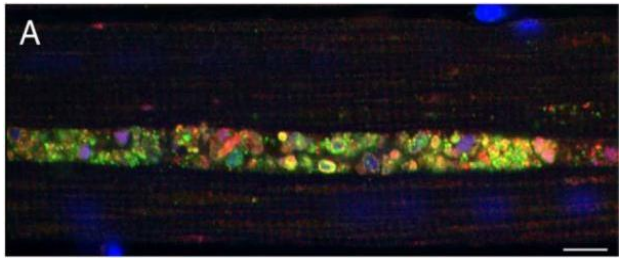


Hugely expanded LAMP2+ lysosomes throughout the fibre (with loss of contractile elements)
Few LC3+ autophagosomes

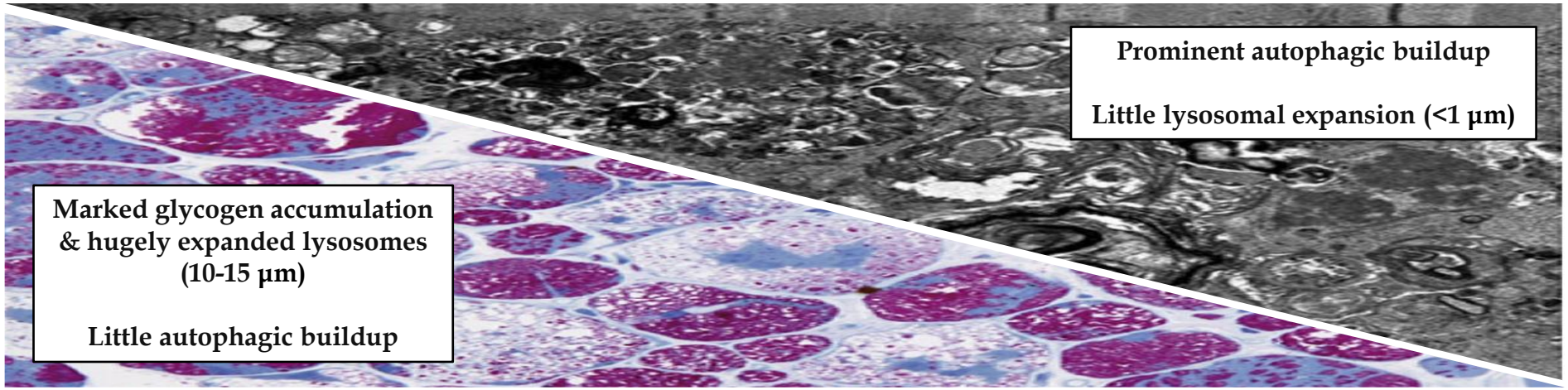


AUTOPHAGIC BUILDUP IN FIBRE OF INFANT ON ENZYME REPLACEMENT
LAMP2+ lysosomes / LC3+ autophagosomes

Late onset



Large clustered LAMP2+ lysosomes &
LC3+ autophagosomes in core of muscle fibre



Muscle biopsy findings in late-onset cases

Different muscle groups and even fibers within the same muscle group exhibit **high variability in the extent and severity** of pathology, especially in late-onset cases

A normal biopsy does not rule out the disease if the "wrong" muscle is sampled

Vacuoles may be extensive or very difficult to find; mainly type 1 fibres, or both types

No correlation of vacuole numbers and disease severity

PAS+/-D staining becomes less sensitive

Increased lysosomal activity

Increased acid phosphatase

Increased immunoreactivity of lysosomal associated membrane protein 2 (*LAMP*2)

Autophagic vacuoles; lipofuscin accumulation

Mitochondrial abnormalities

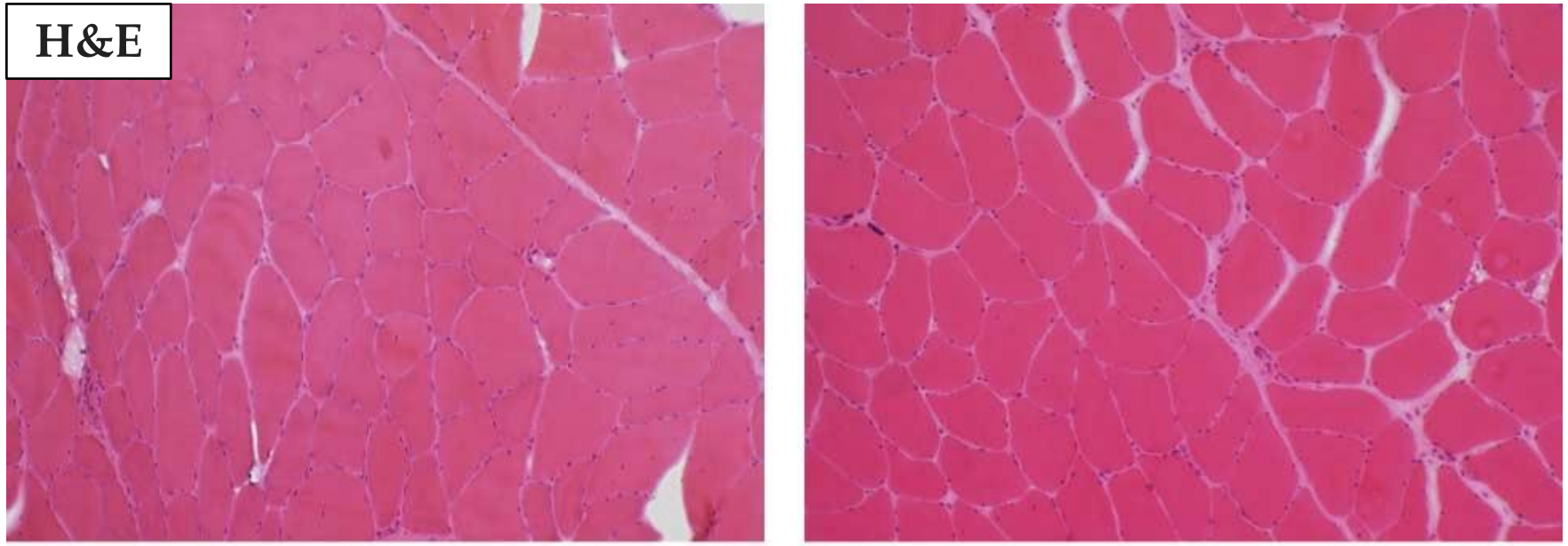
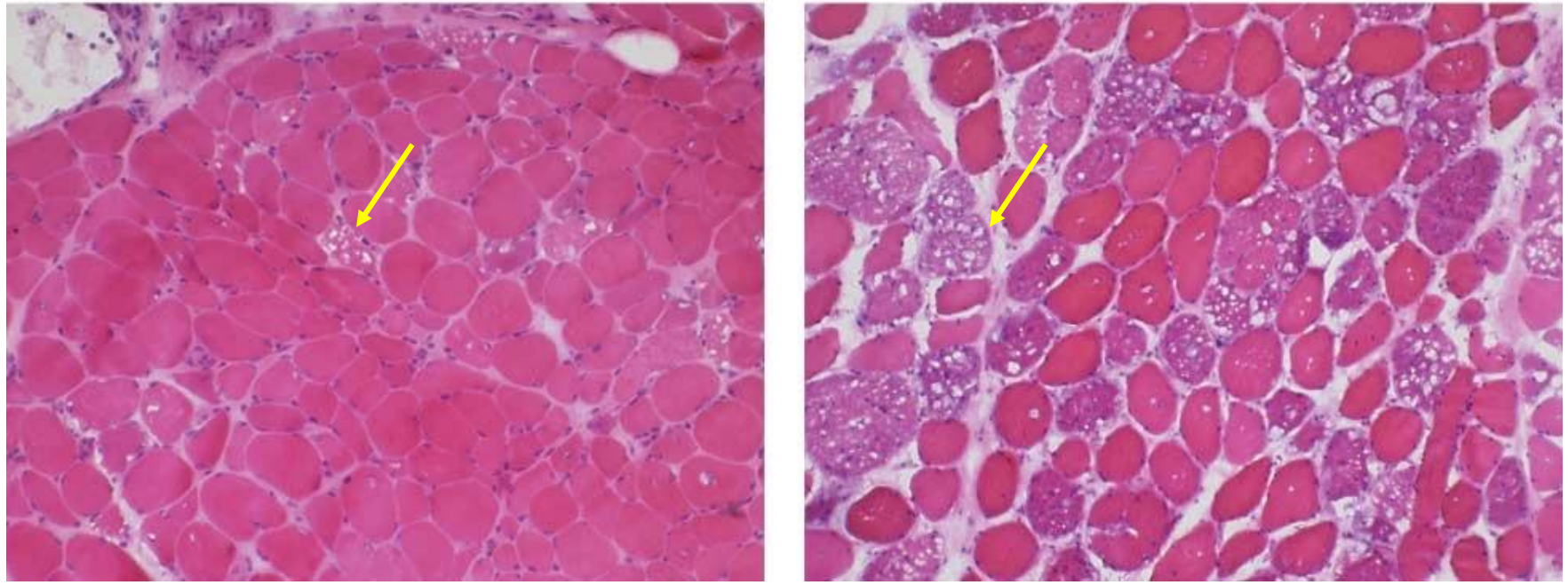
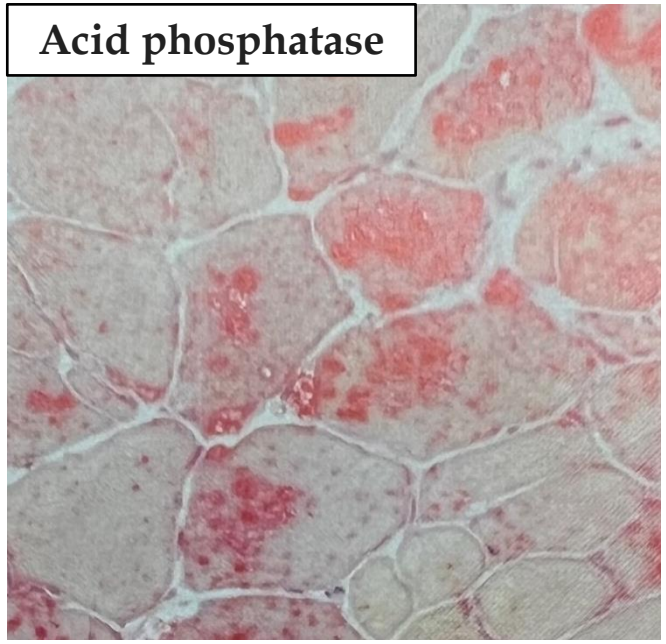


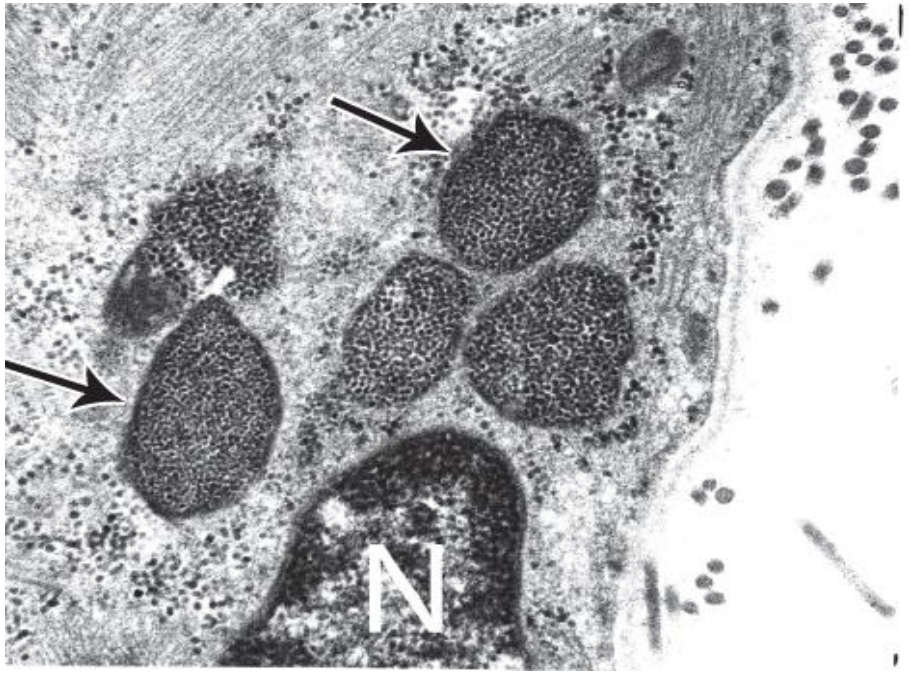
Fig. 1. Vissing et al. *JAMA Neurol*. 2013;70(7):923-927.





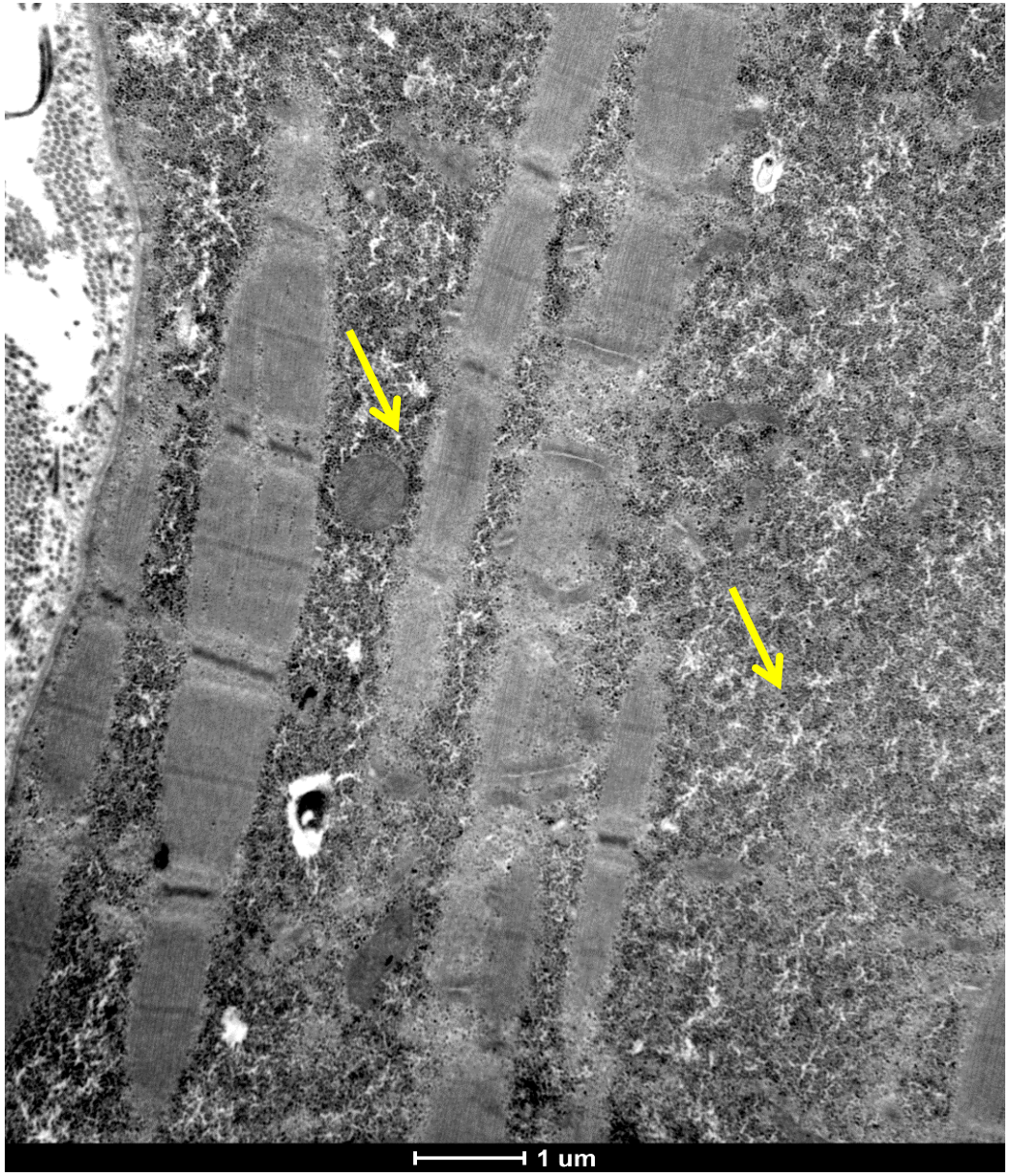
Muscle Biopsy: A Practical Approach, 5e, 2021

Electron microscopy



Principles of Rubin's Pathology, 7e, 2019

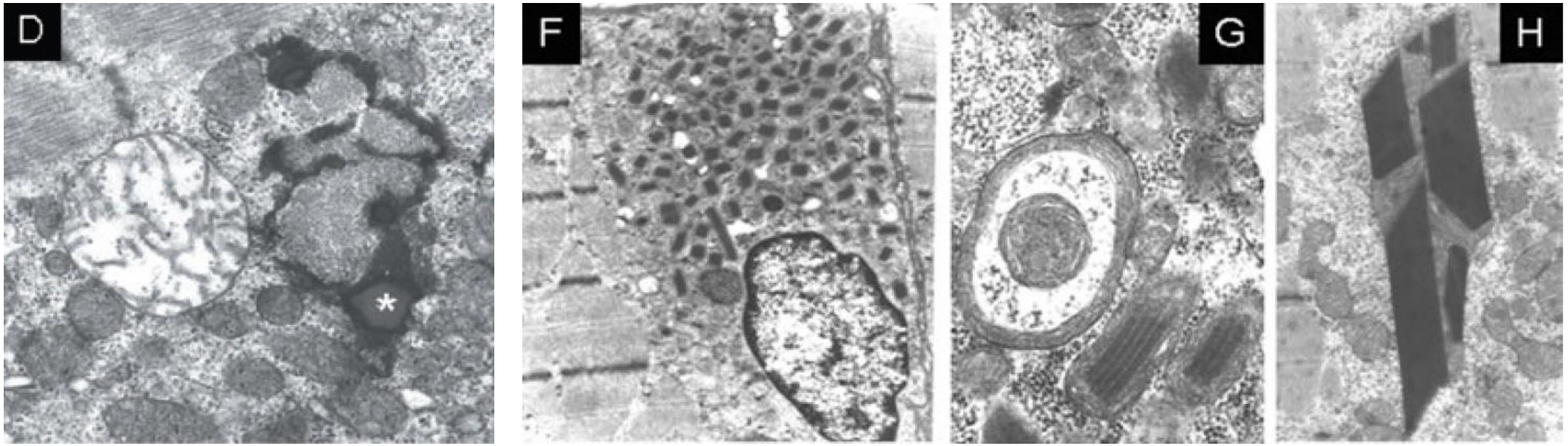
Membrane-bound (intralysosomal) glycogen



Extralysosomal glycogen

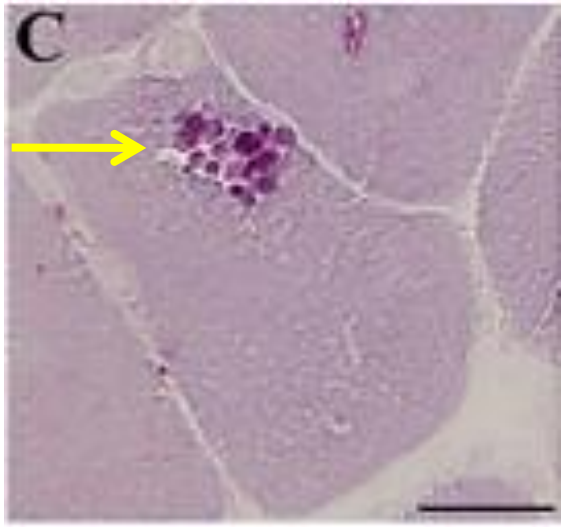
Electron microscopy

Abnormal mitochondria and paracrystalline inclusions (non-specific)

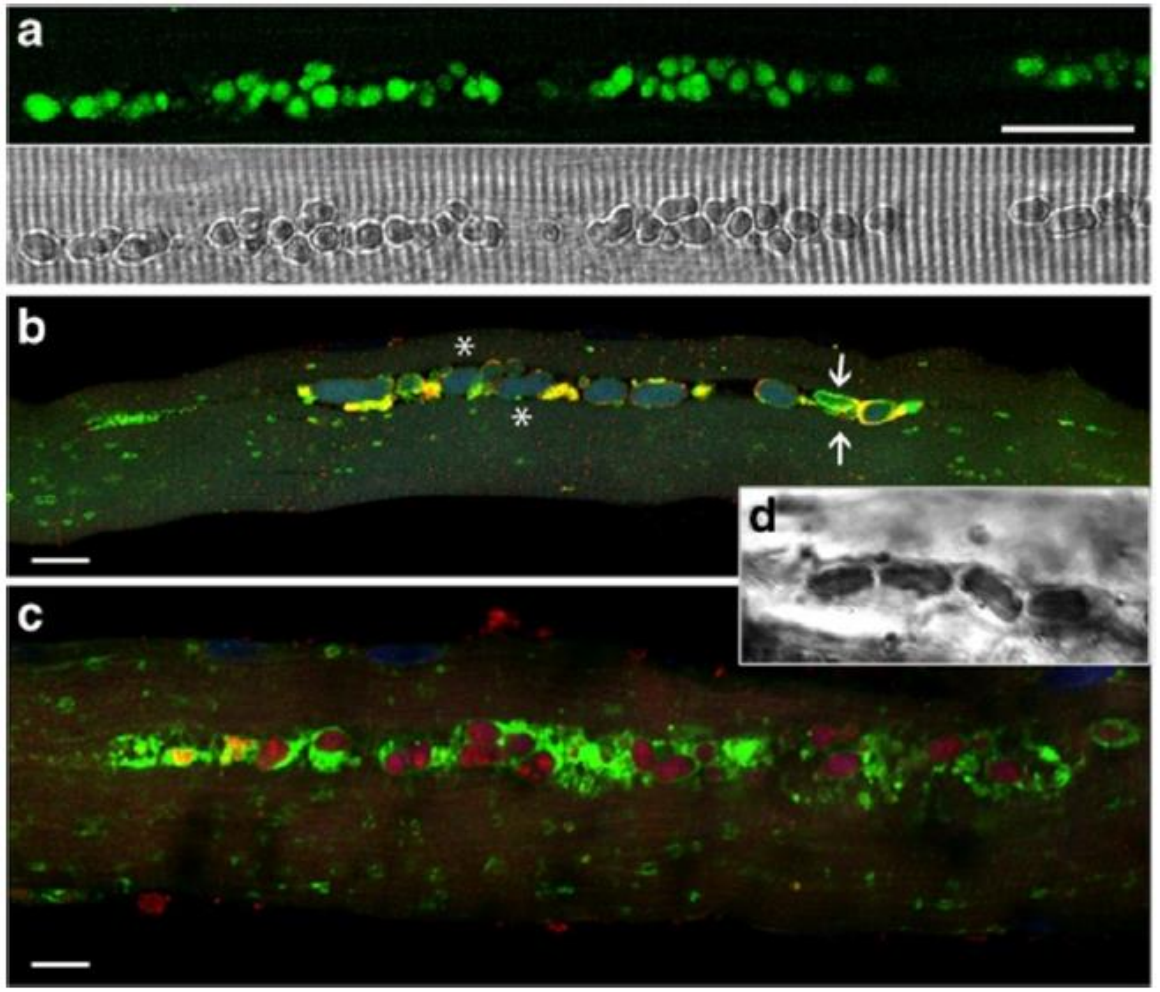


B. G. H. Schoser et al. *Neuropathology and Applied Neurobiology* (2007), **33**, 544–559

Lipofuscin



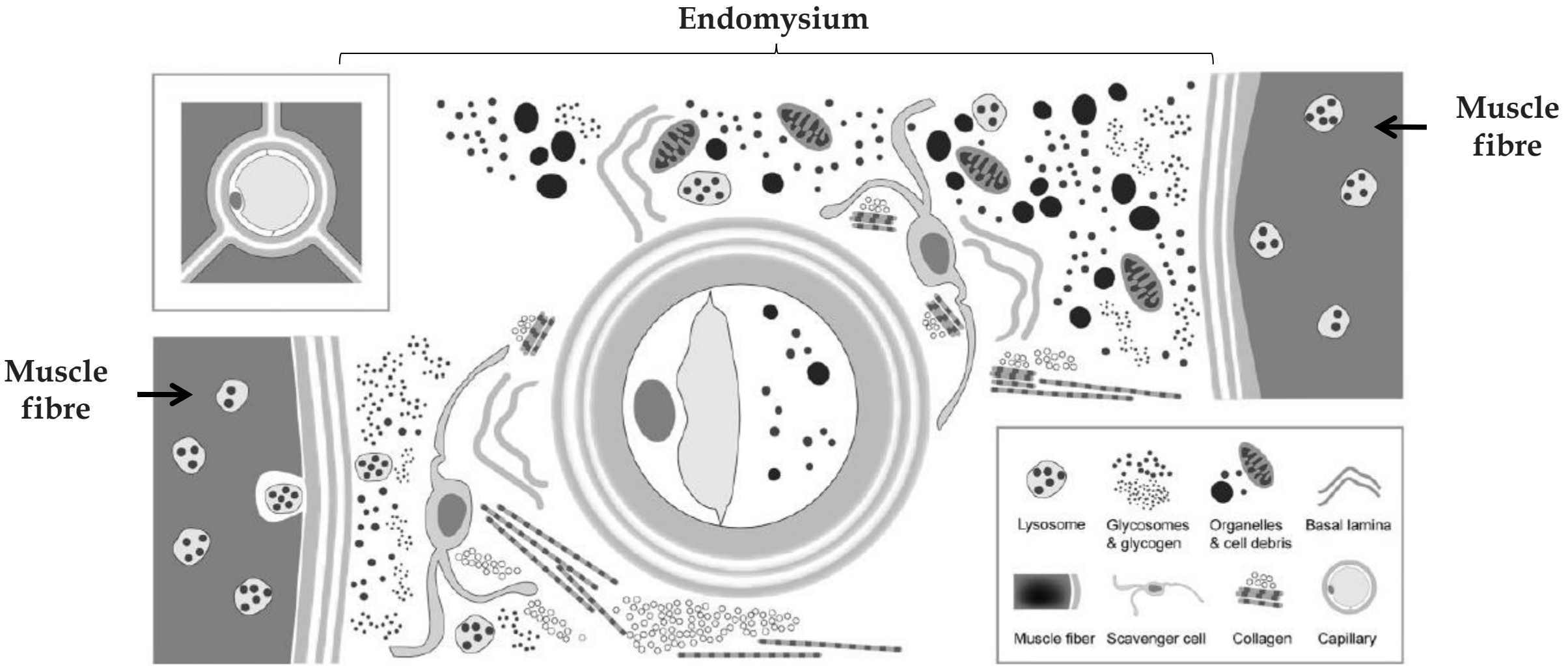
Acid phosphatase-positive globular inclusions
Tsuburaya et al. Neuromuscul Disord 22 (2012) 389–393.



Confocal fluorescent imaging
Feeney et al. Acta Neuropathologica Communications 2014, 2:2.

Endomysial stromal and capillary pathology

Buckley et al. **Outside the fiber: Endomysial stromal and capillary pathology in skeletal muscle may impede infusion therapy in infantile-onset Pompe disease**.
J Neuropathol Exp Neurol. 2023 Mar 20;82(4):345-362.



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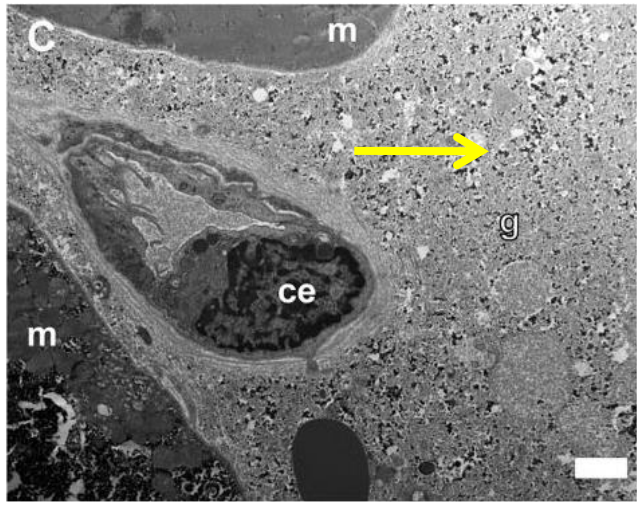
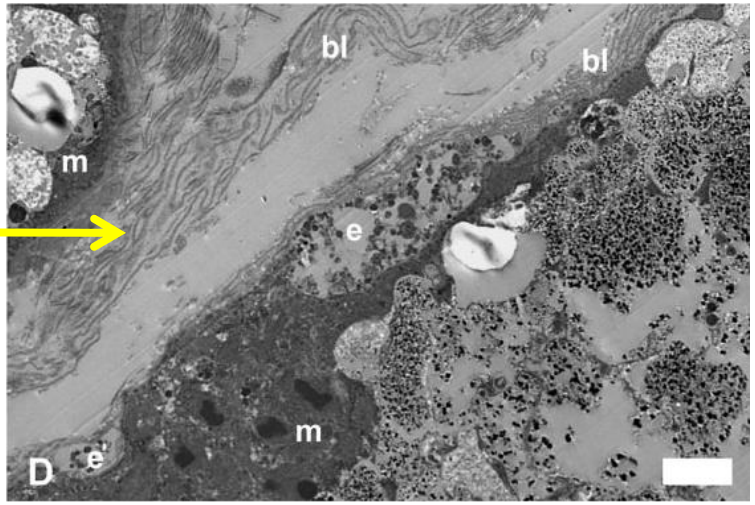
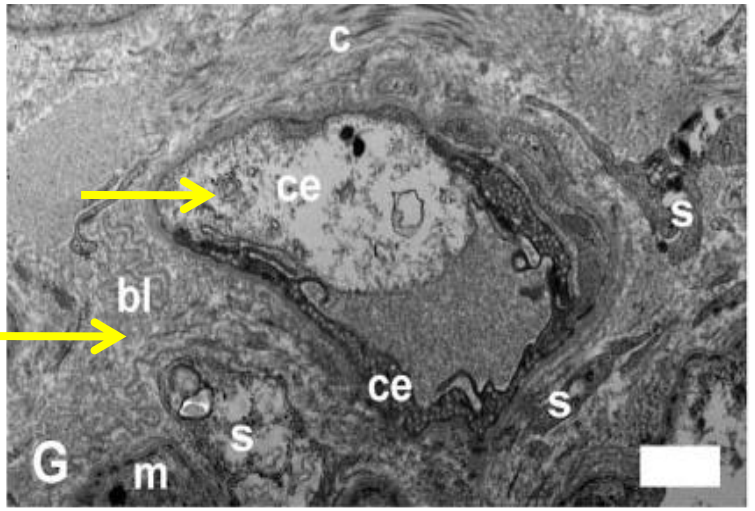


Expansion of endomysium due to presence of lysosomal material, glycosomes/glycogen, cellular debris, and organelles from exocytosis or fibre lysis



Basal laminar reduplication and/or expansion of muscle fibres & capillaries



Hypertrophy and degeneration of capillary endothelial cells with narrowing of vascular lumen

Physical obstacles to delivery of infused ERT from blood to skeletal muscle fibres

m = muscle fibre
bl = basal lamina
ce = capillary endothelial cell
s = scavenger cell
c = collagen

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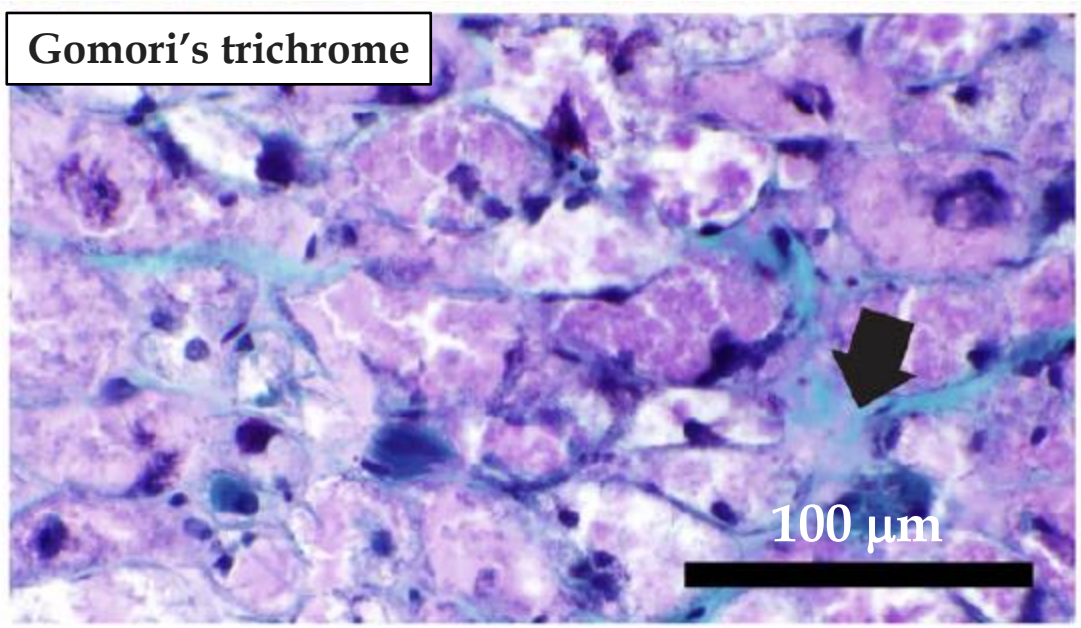

Summary

Understanding pathophysiology is important in explaining histopathological findings, and vice versa.

Because of the availability of alternative / non-invasive diagnostic tests, the classical picture of Pompe disease in muscle biopsies is rarely seen in clinical practice.

Vacuolar change can be very subtle and PAS stain has limited sensitivity particularly in late-onset cases.

Type II GSD is an autophagic myopathy - lysosomal markers are helpful.

Muscle biopsy has limited clinical value in routine diagnosis, but offers valuable insight into the pathophysgiology of the disease.