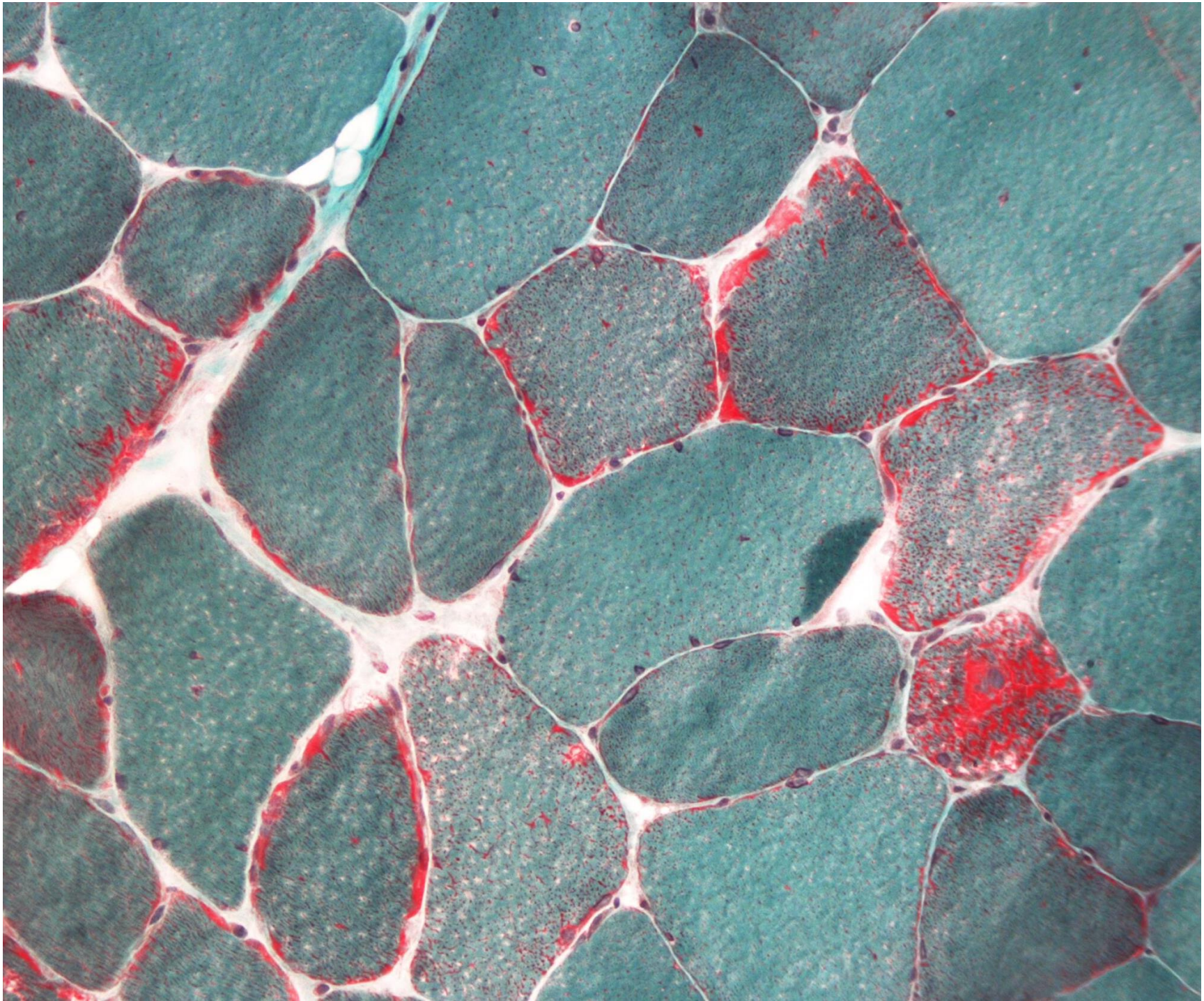
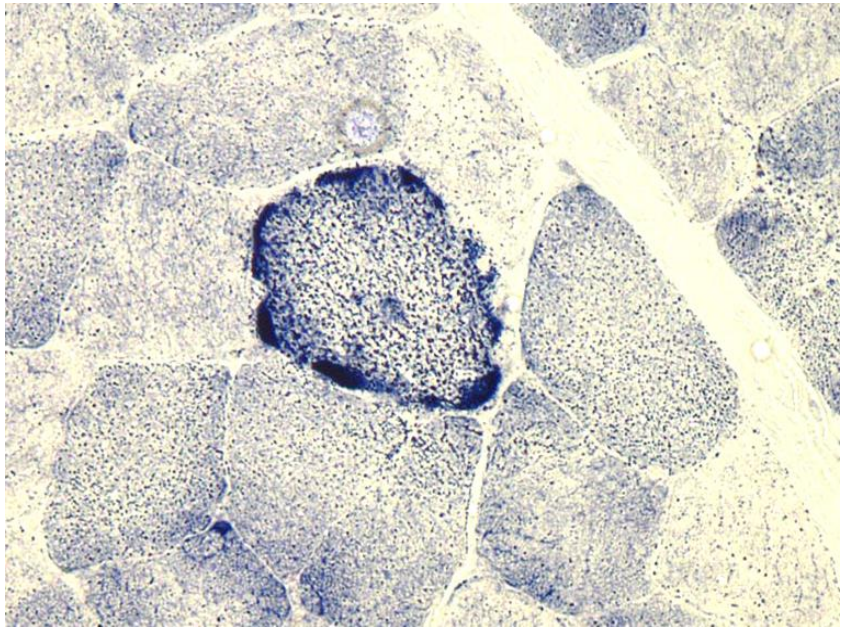
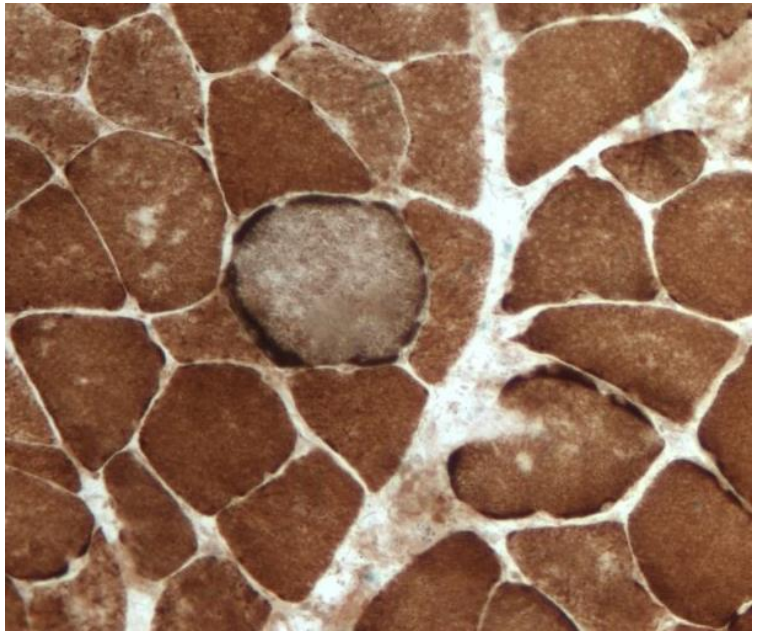
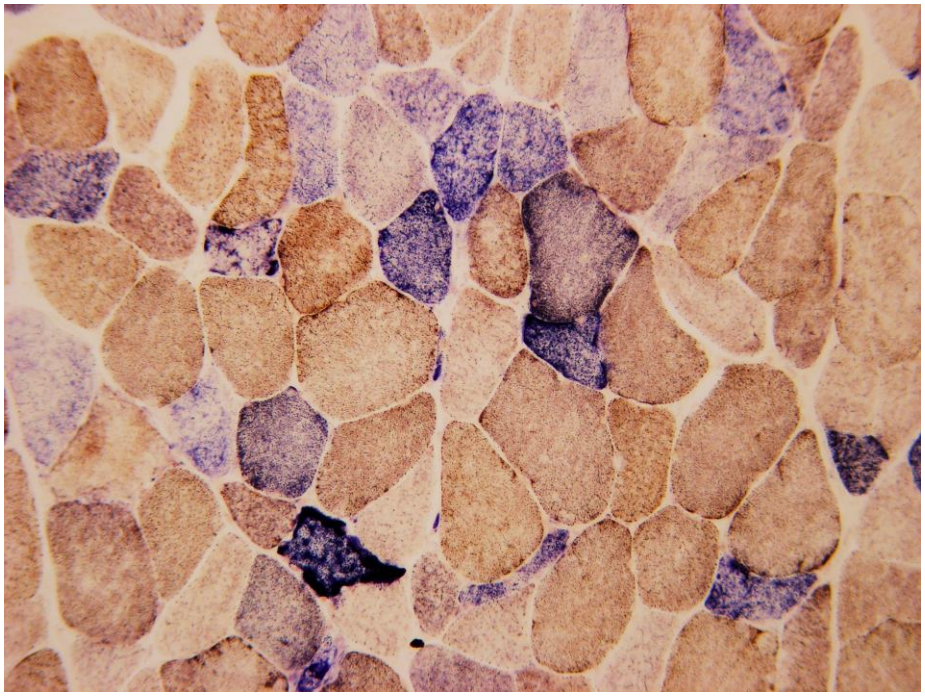
Neuropatologia delle malattie mitocondriali

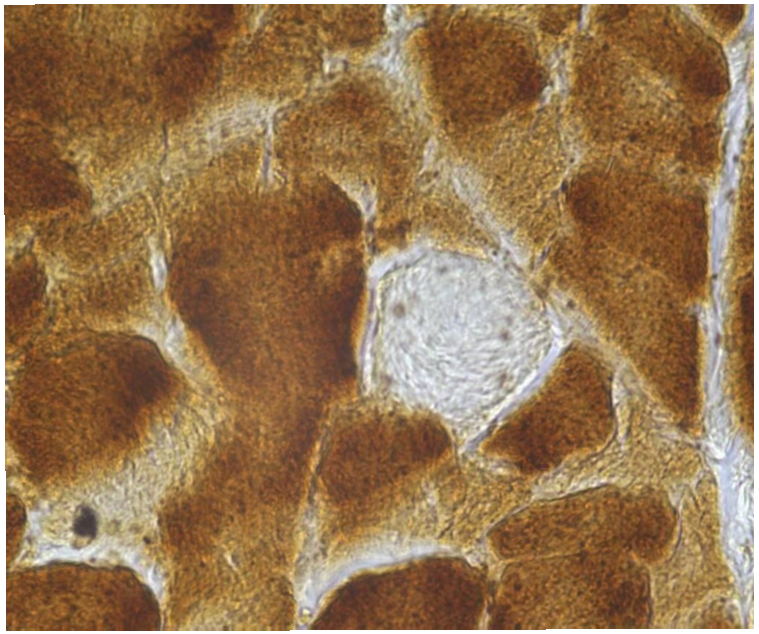
Carla Giordano, Università La Sapienza, Roma

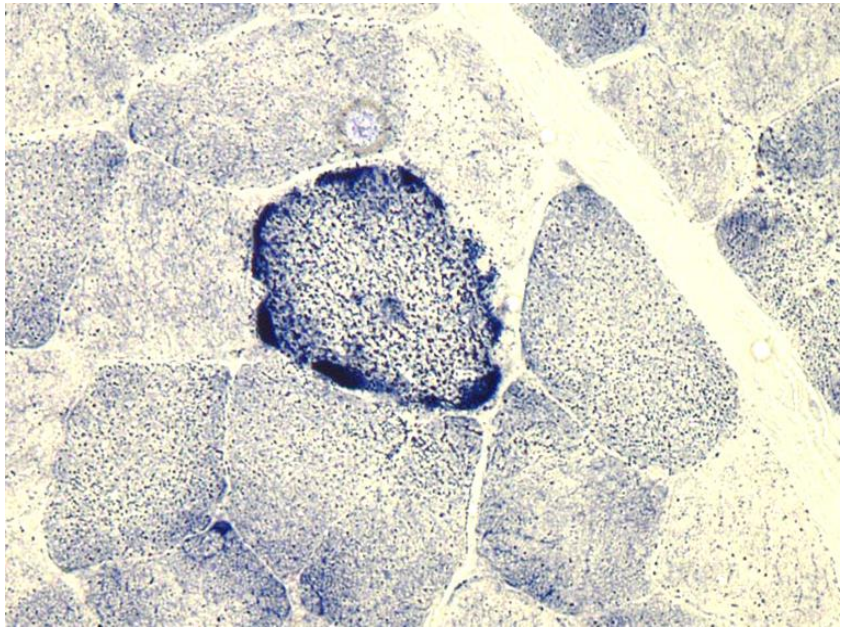


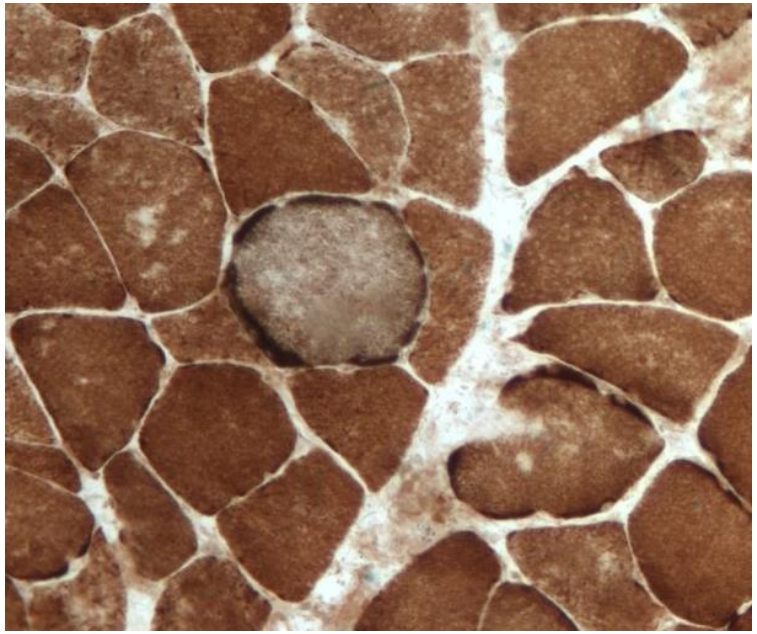


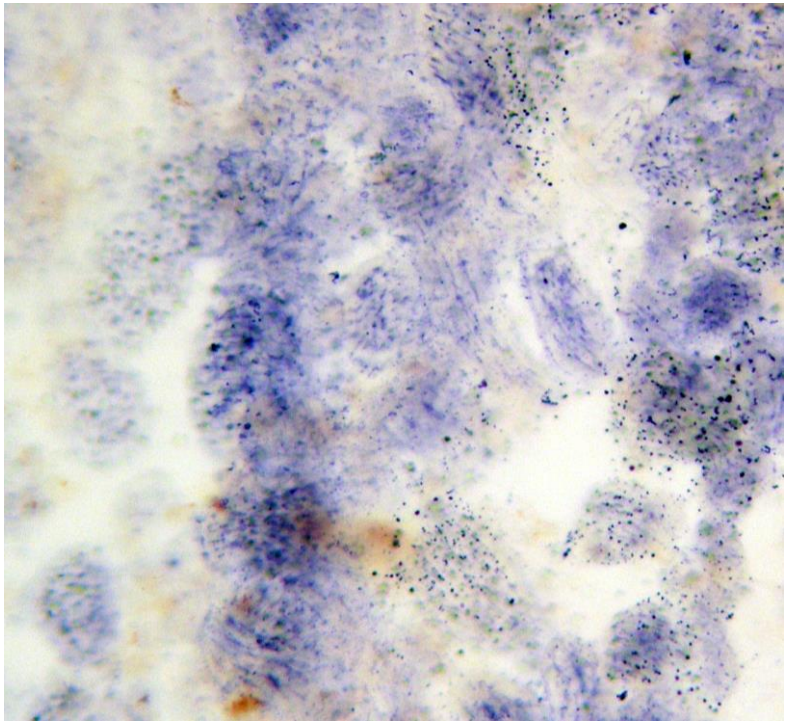


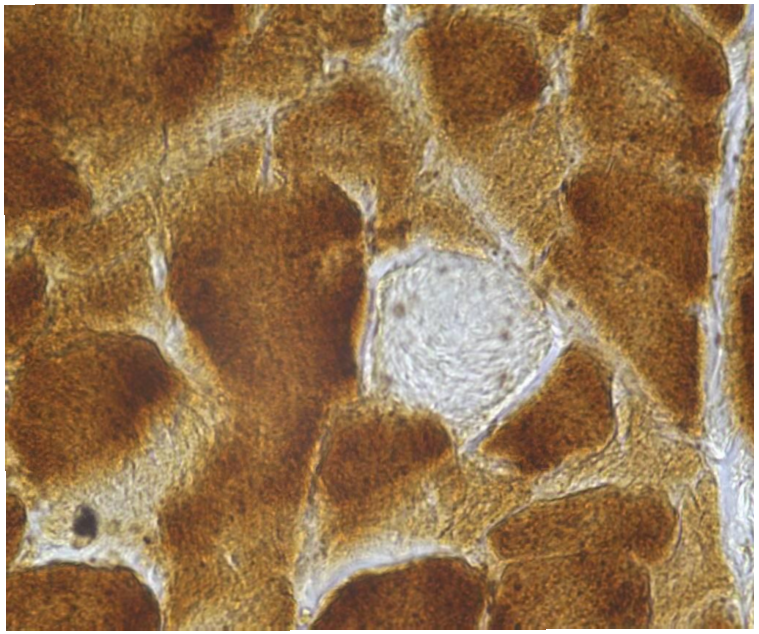


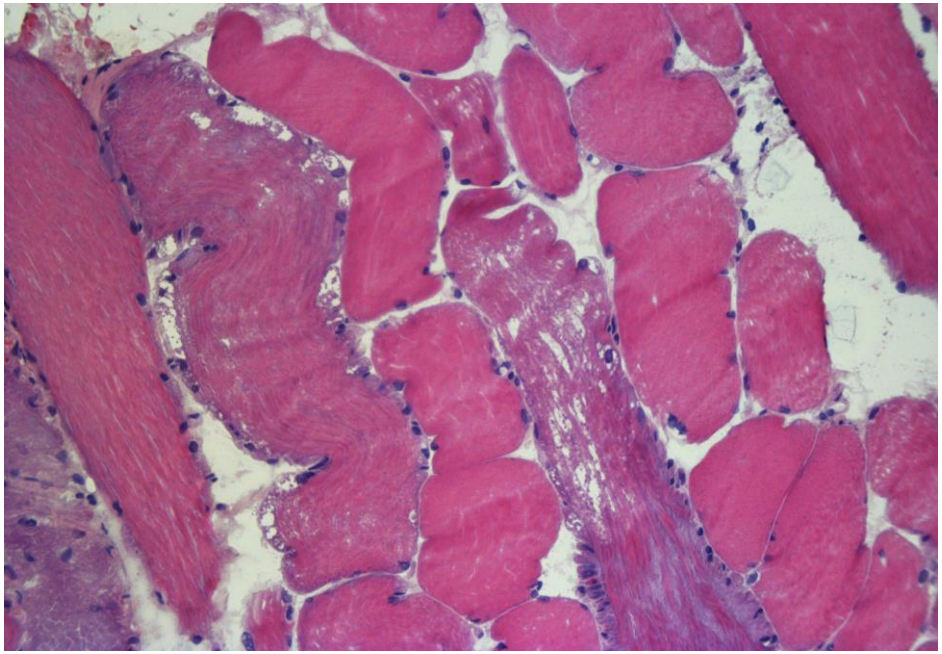


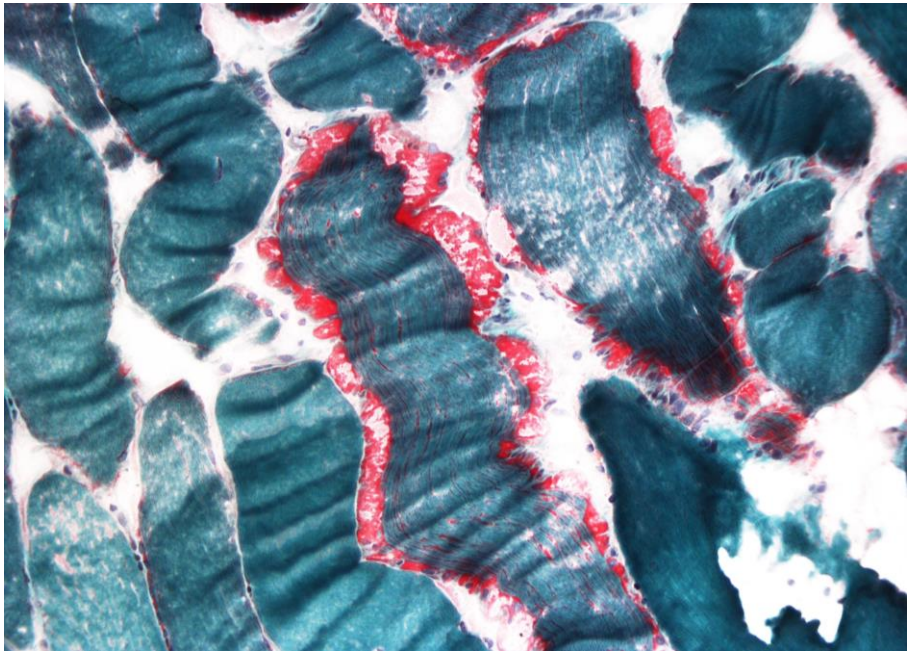


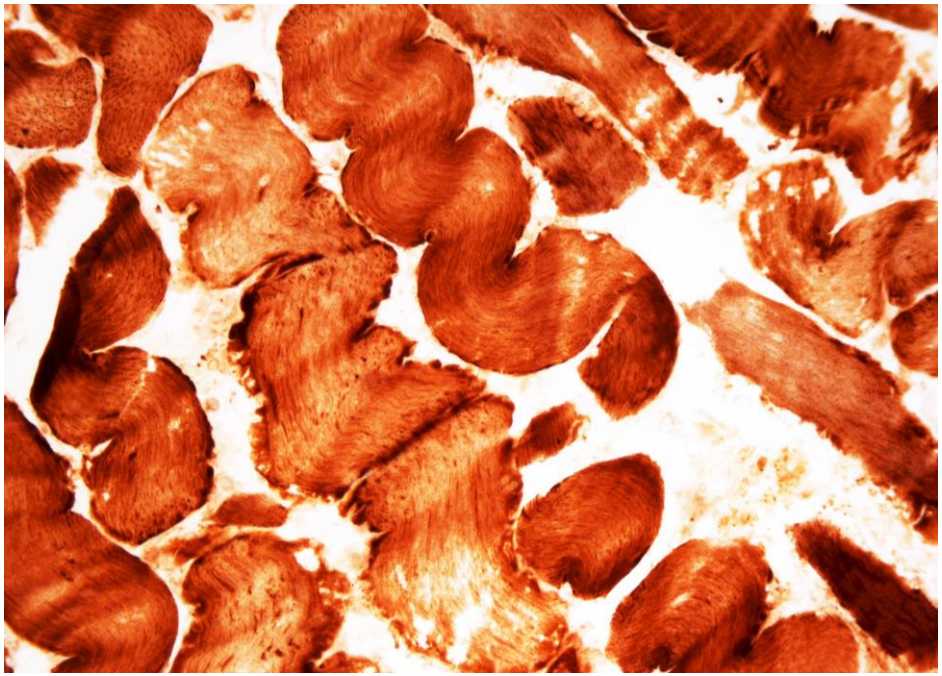




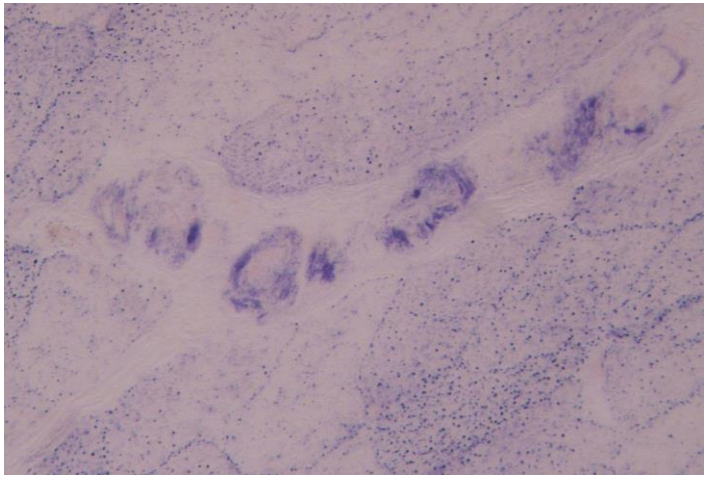


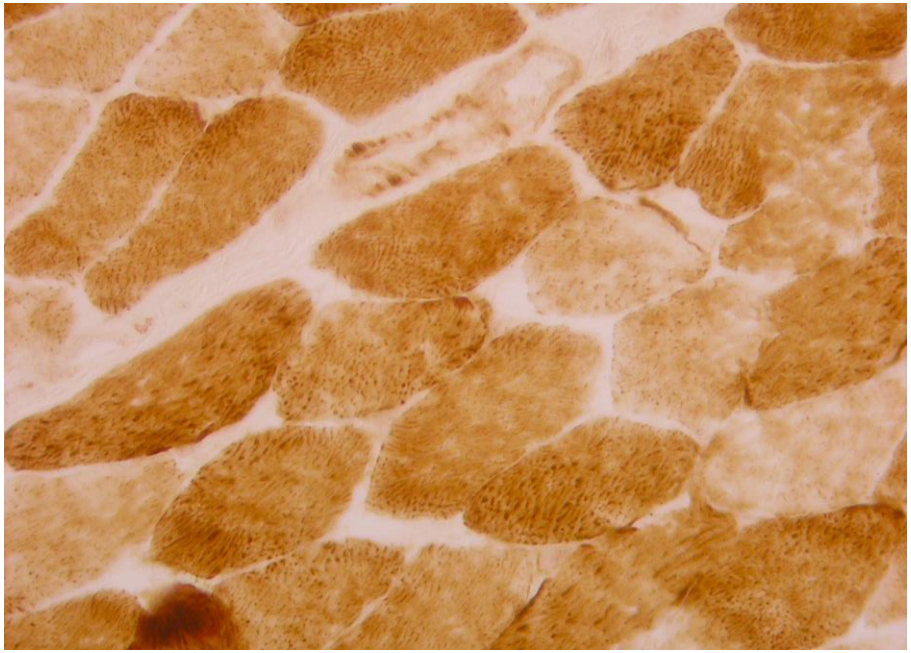


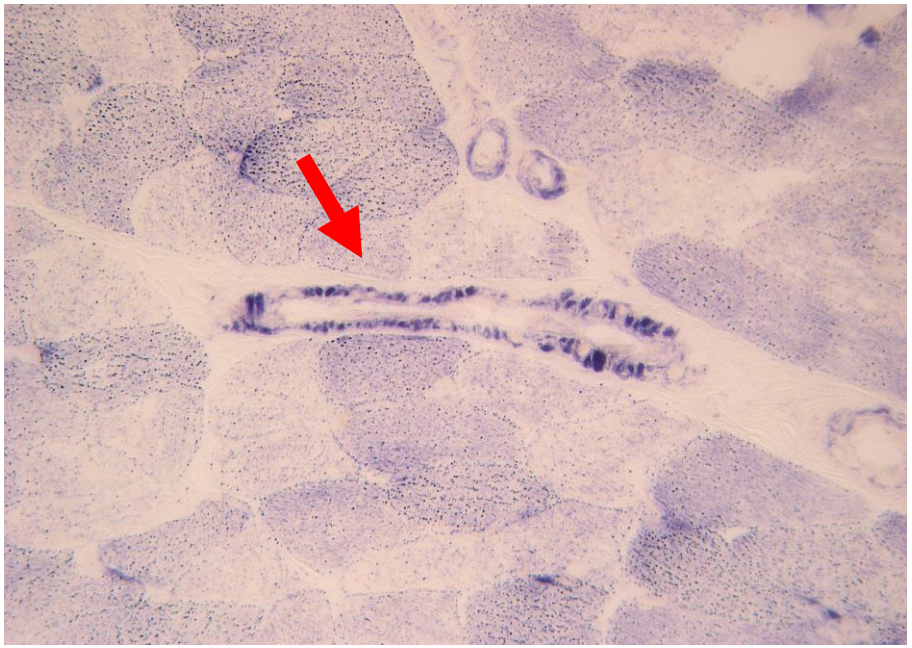




Male, 37 years old, 3243 A>G



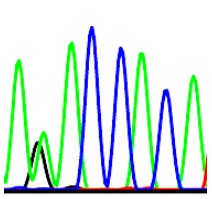




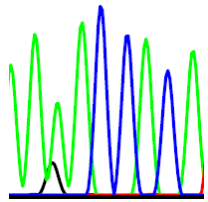
Male, 6 years old ,
Diplopia
Leigh syndrome

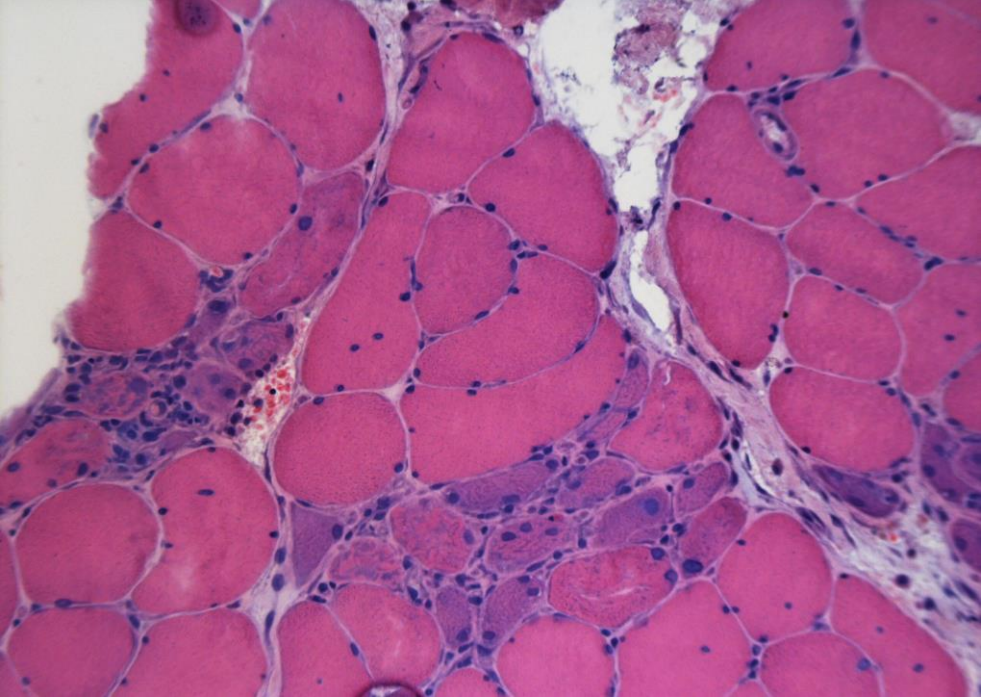
M. 13513G>A, MTND5

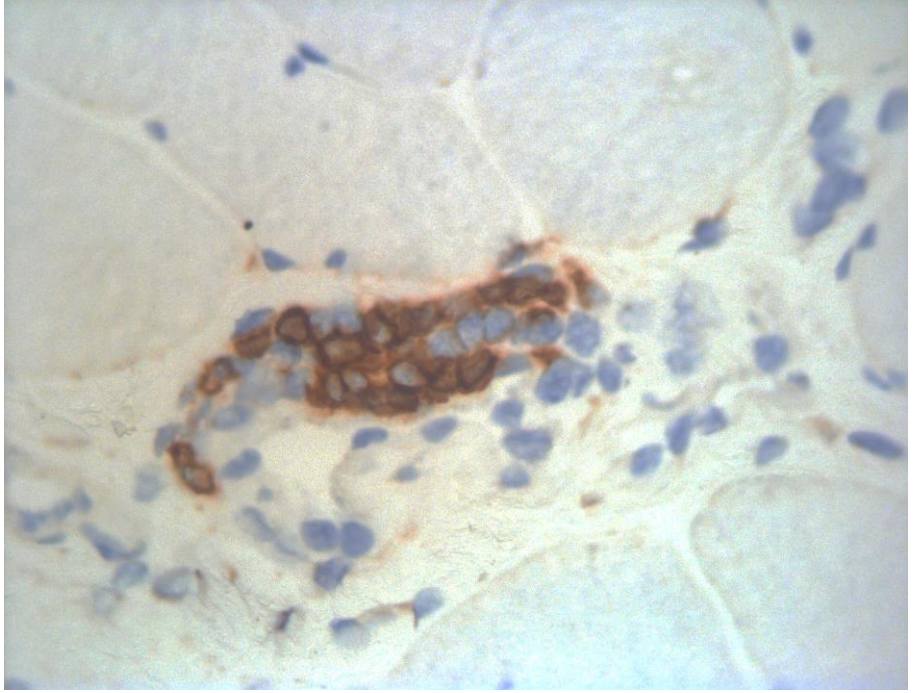
Blood

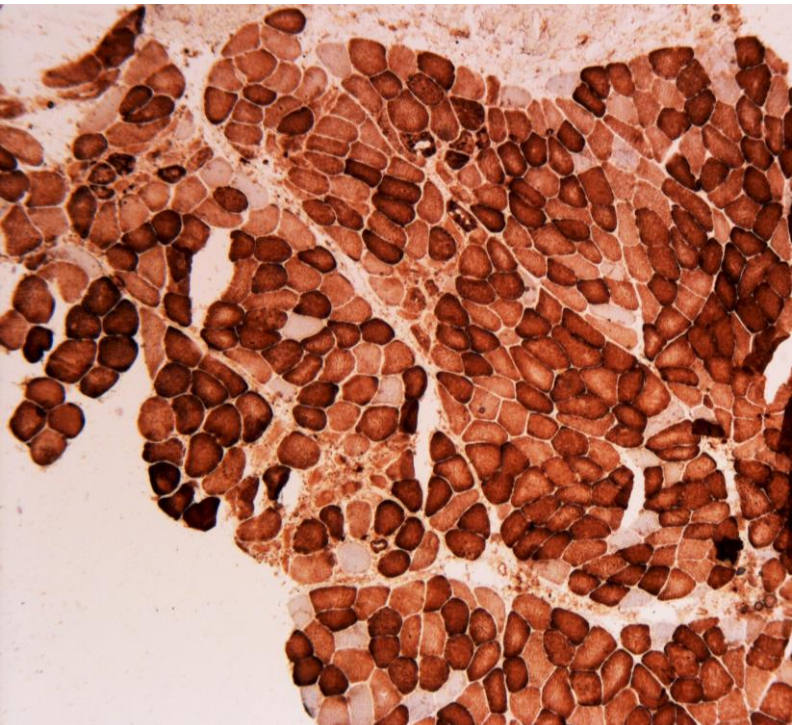


Muscle

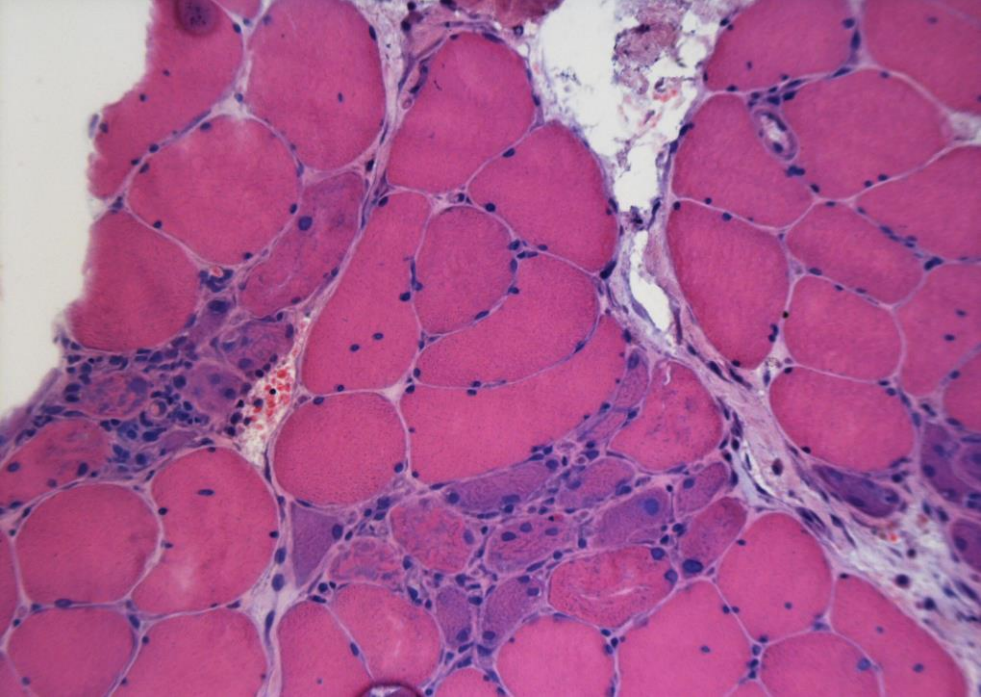


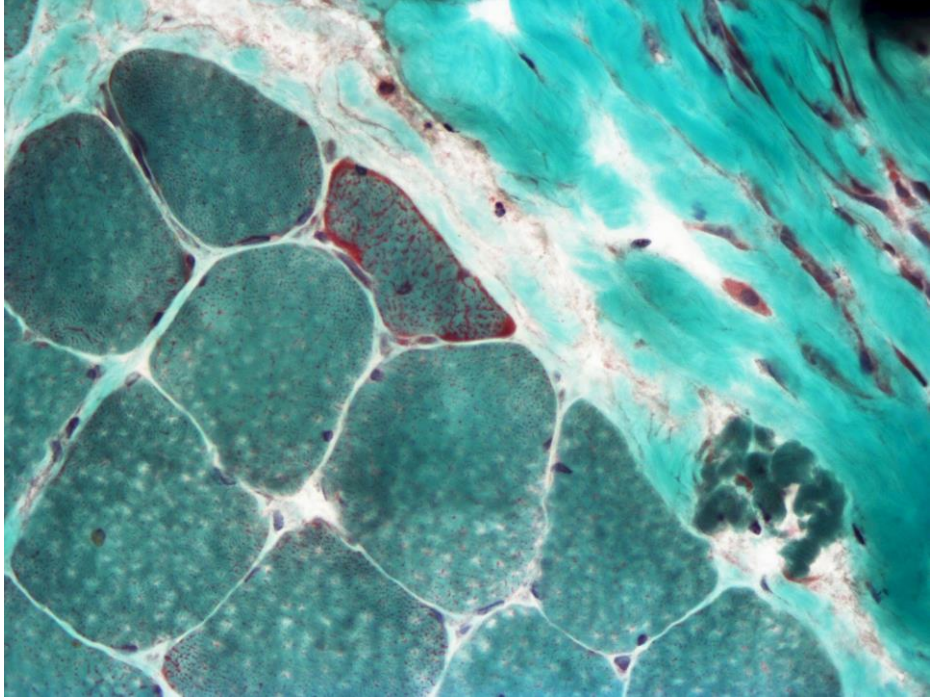


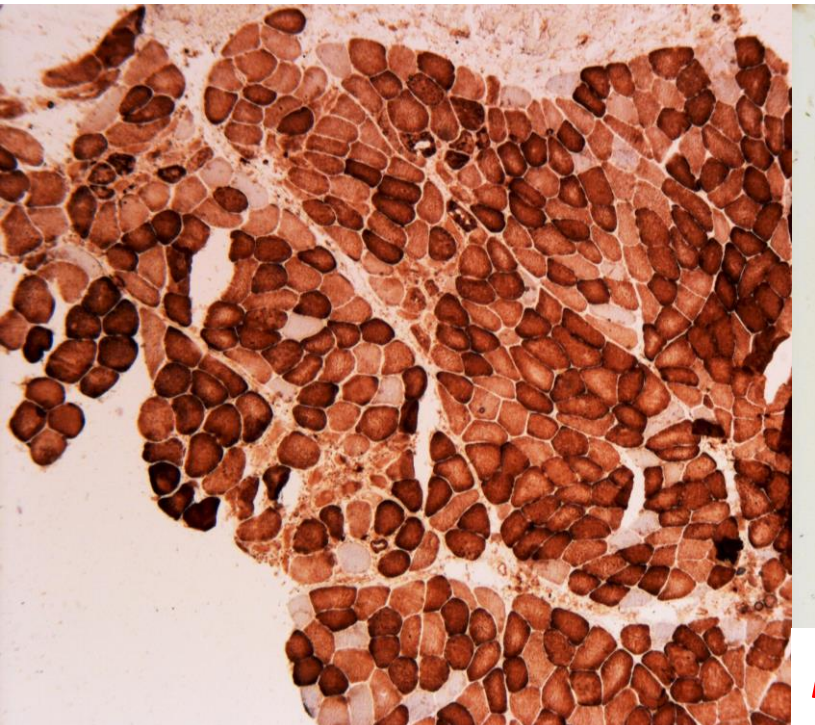


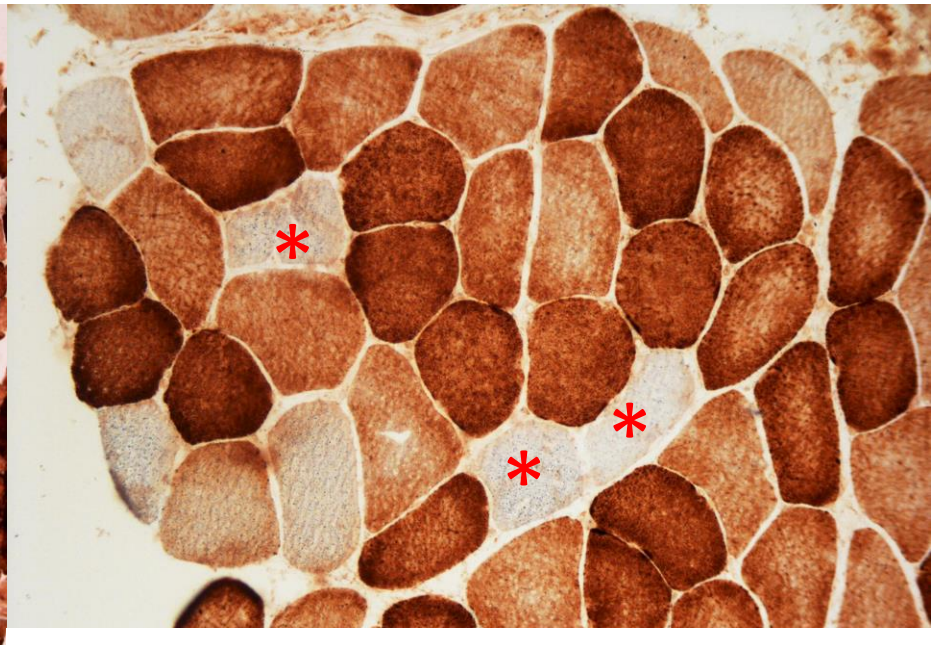


Male, 50 years old,
PEO

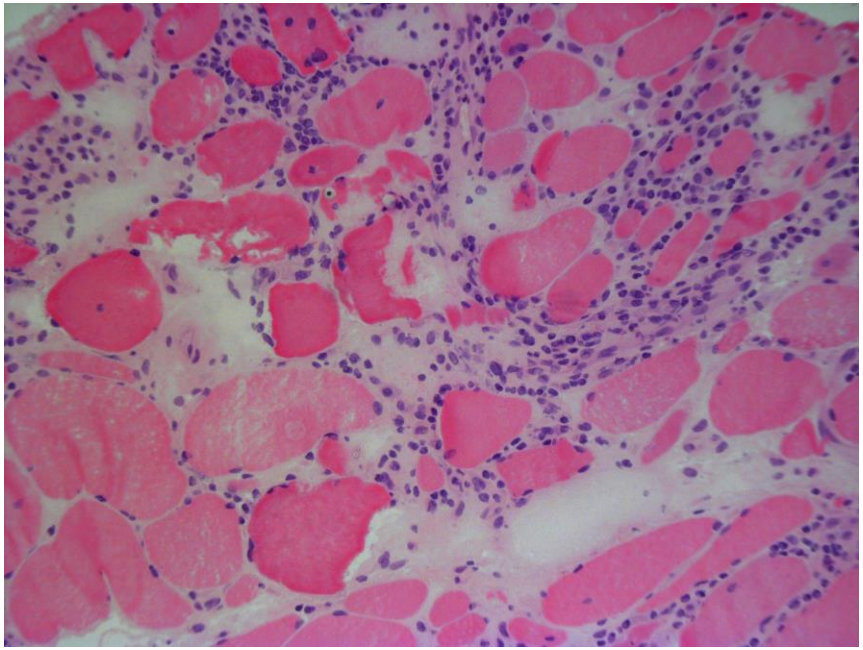




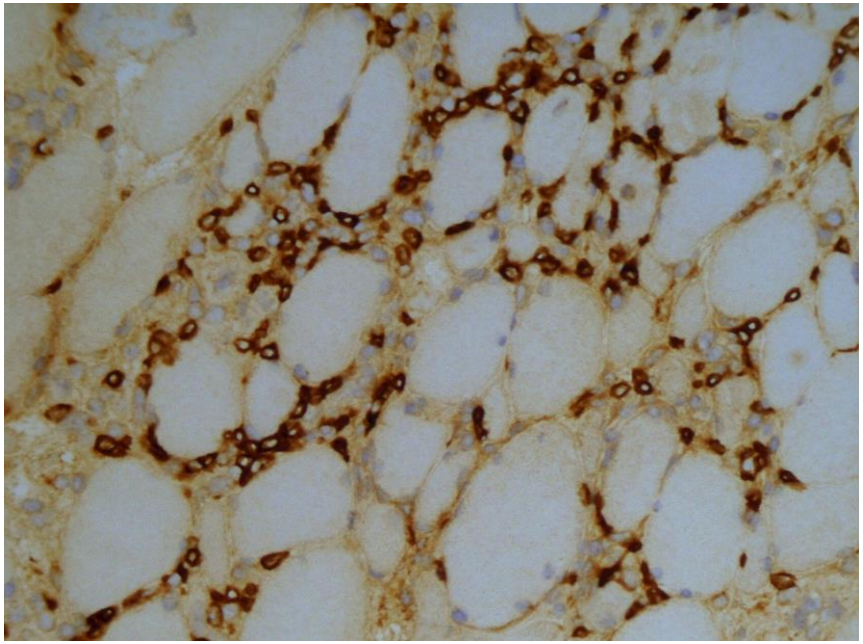


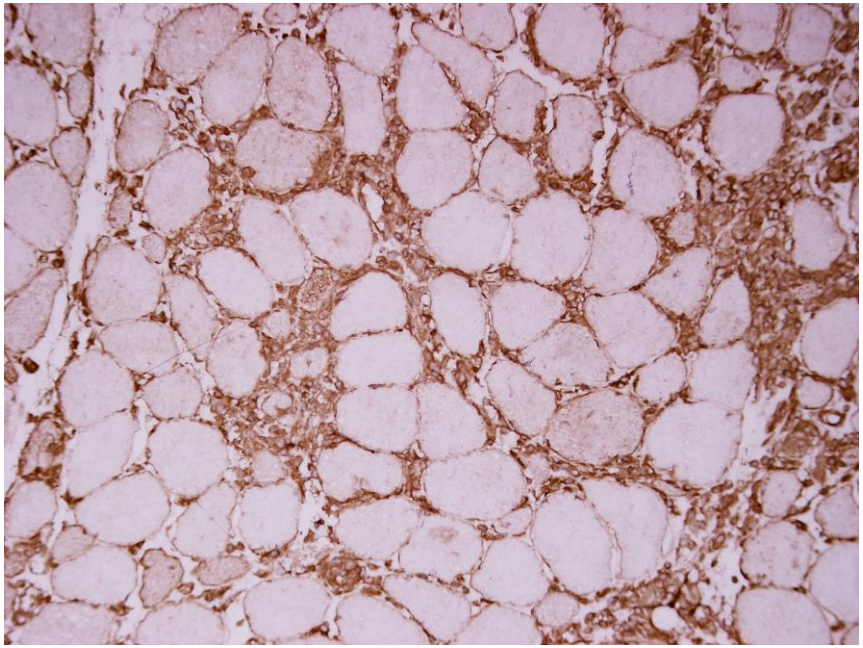


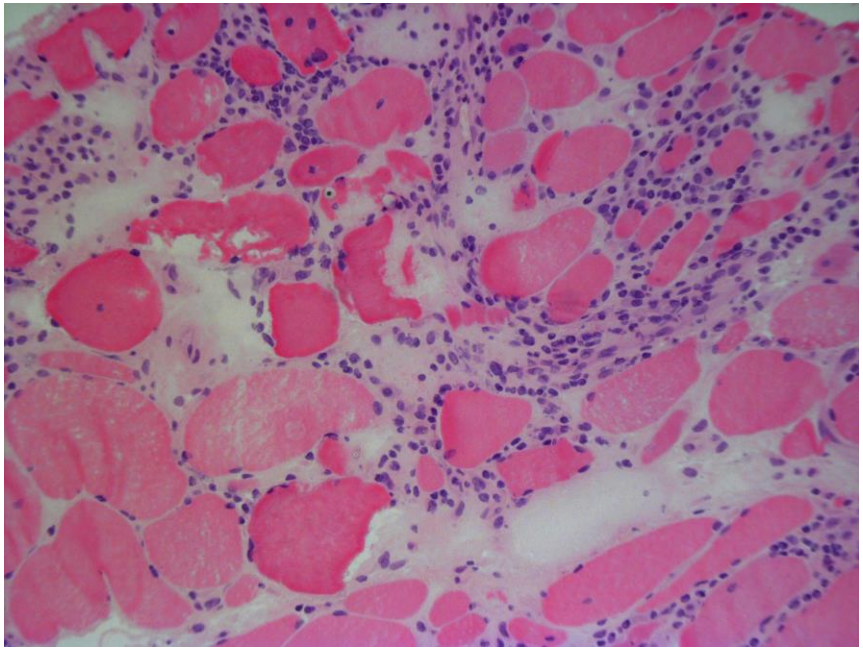
POLG2 heterozygous variant (p.416G>A)

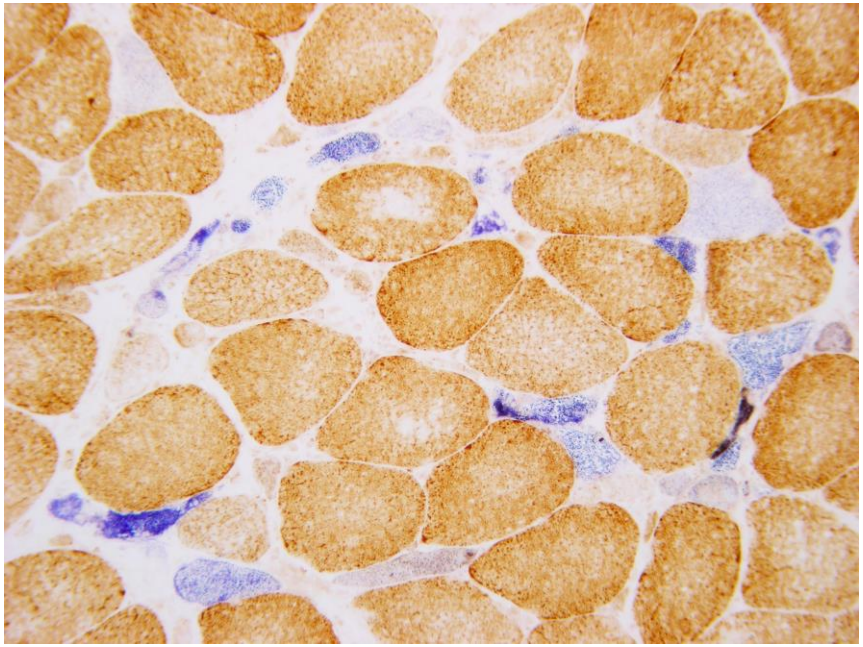


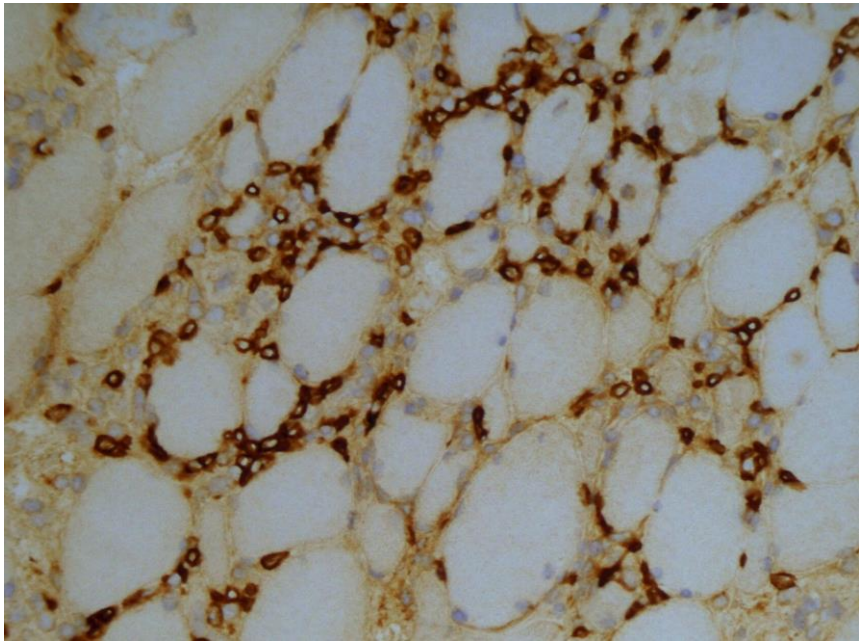
Female, 46 years old, Sjogren syndrome, anti-JO1+,anti Ro SSA+, anti-Ro SSB+, muscle weakness and pain, rhabdomyolysis

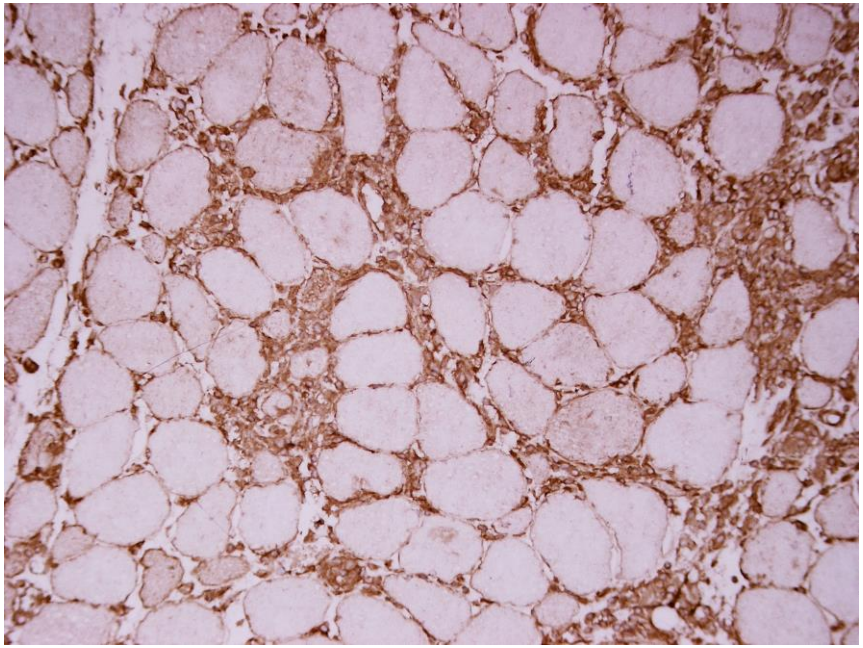


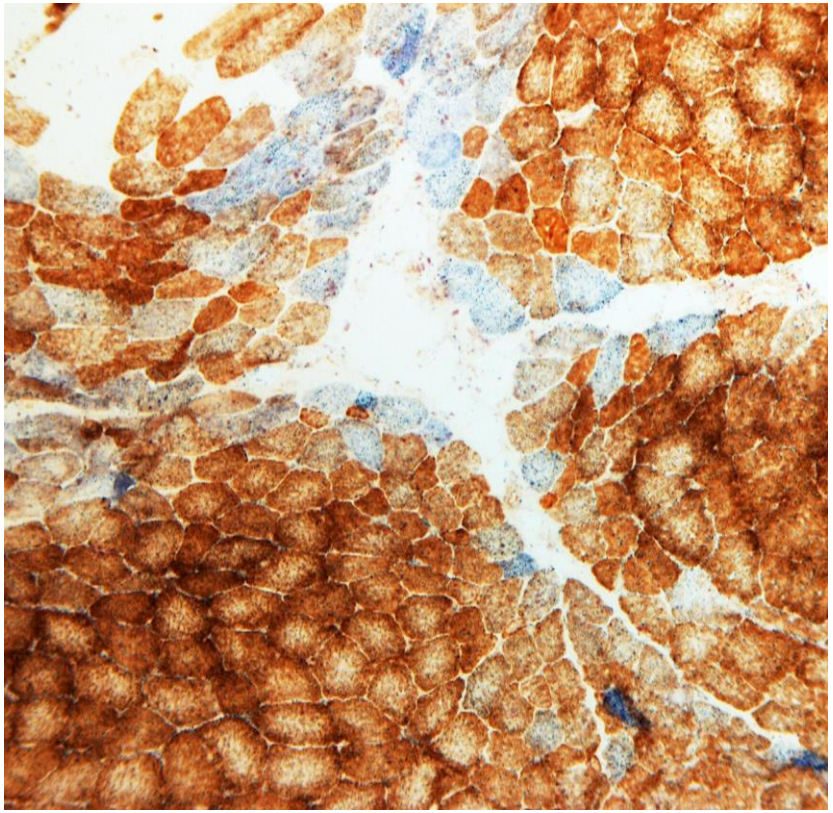


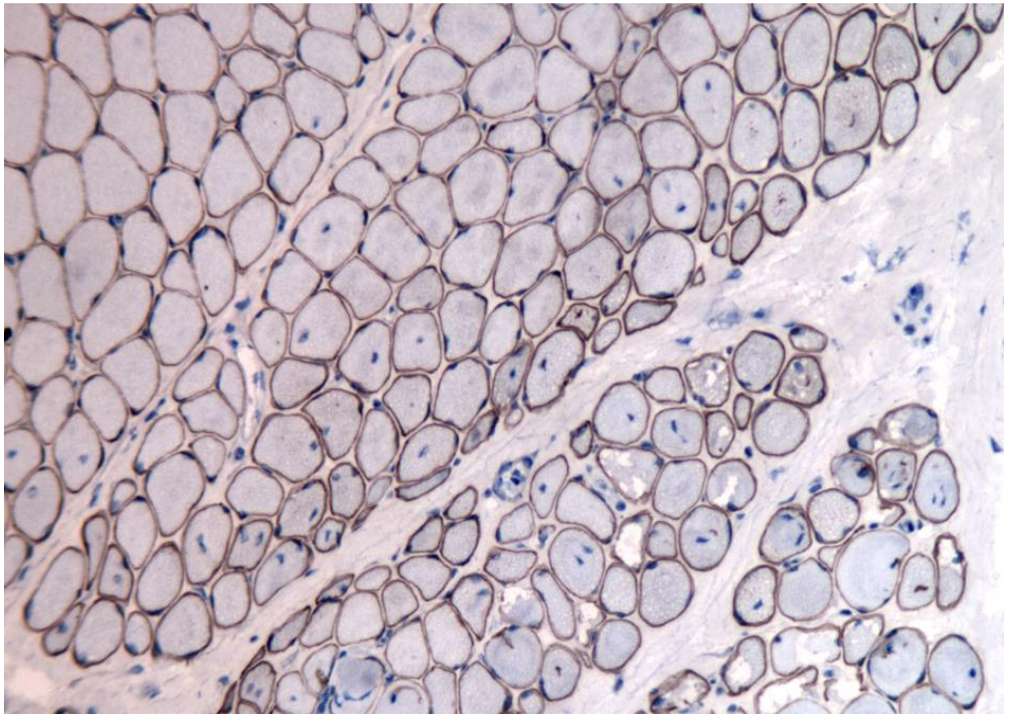


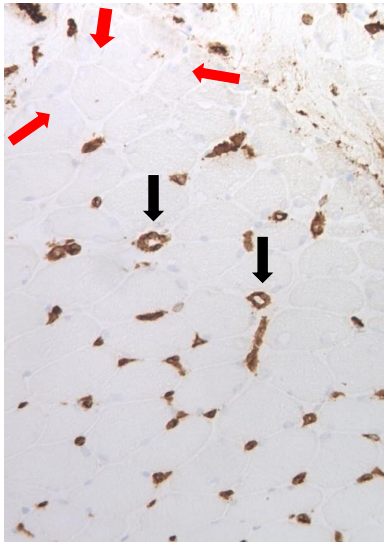


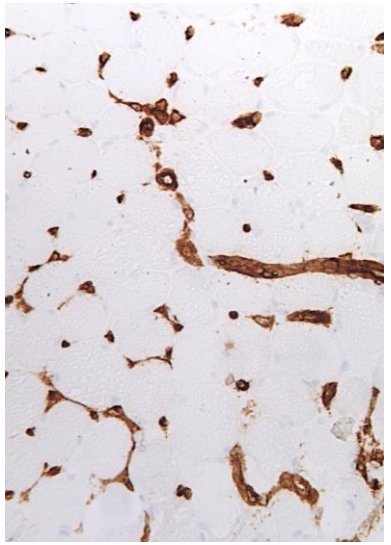




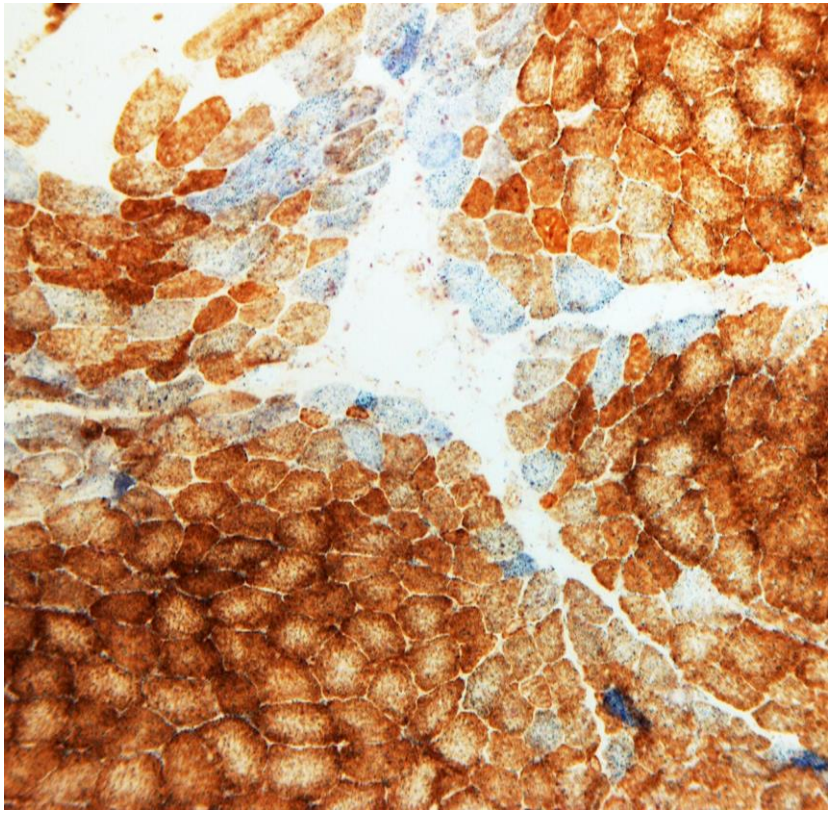


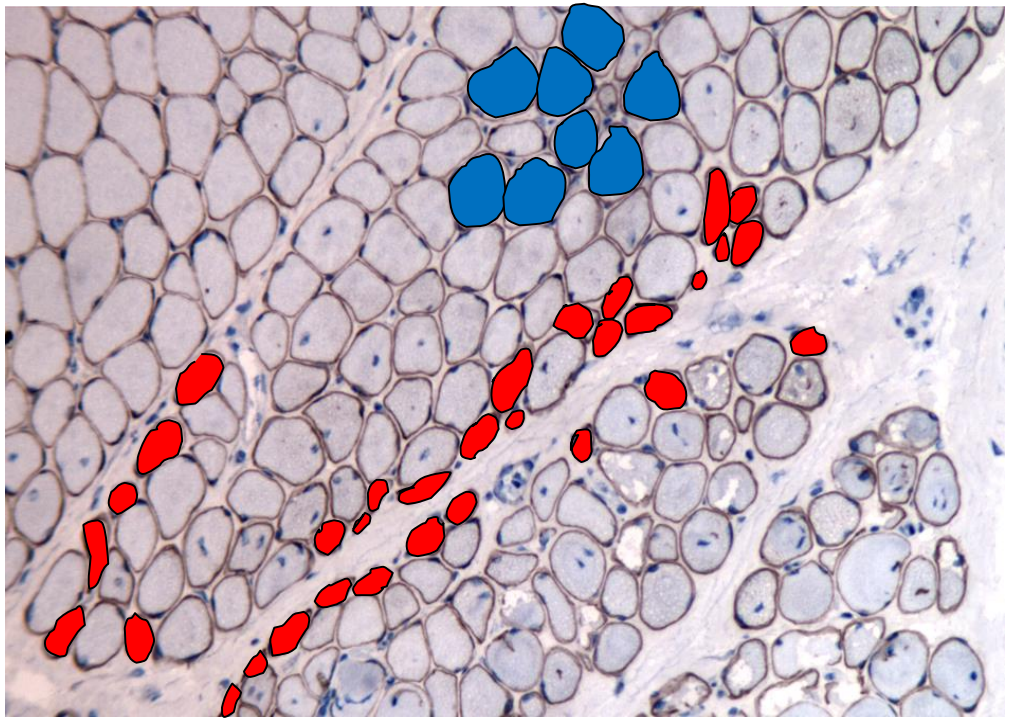






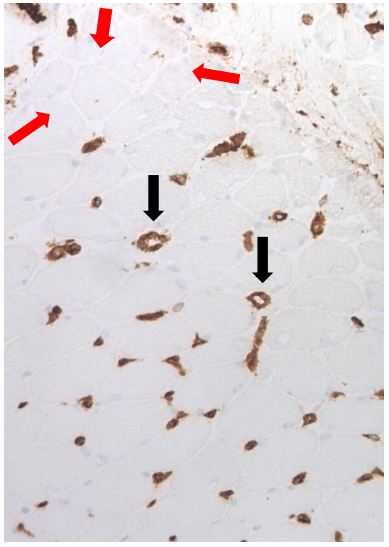
Cerbelli et al. Virchows Archiv (2018) 472:477–487

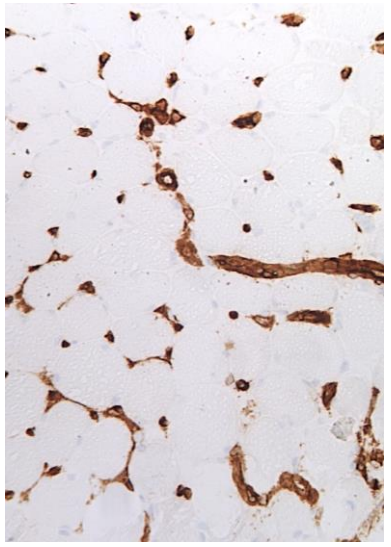




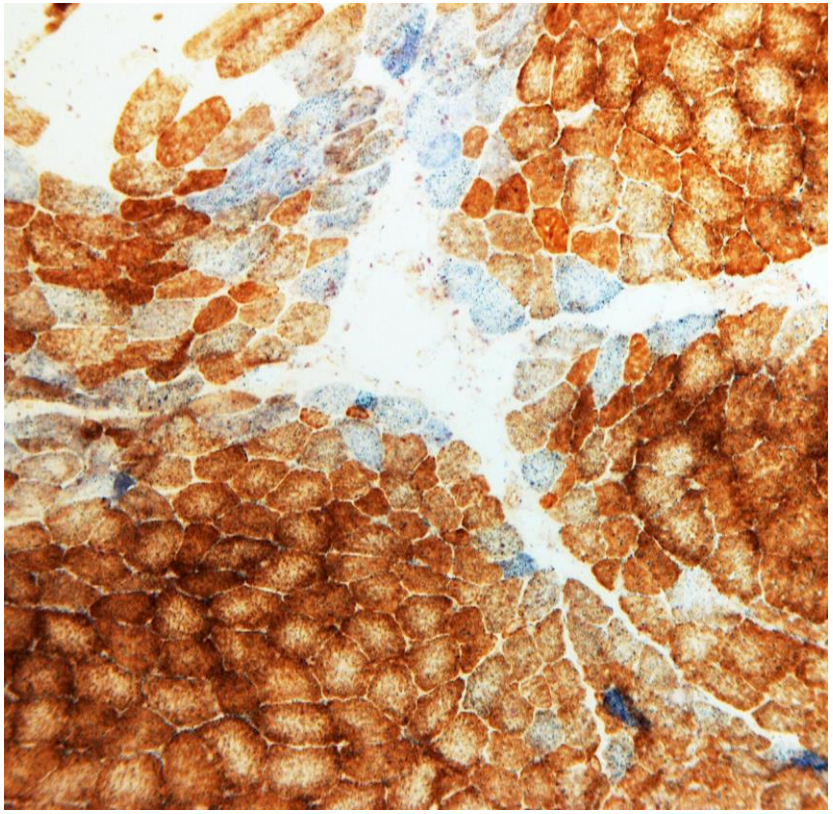
Juvenile Dermatomyositis

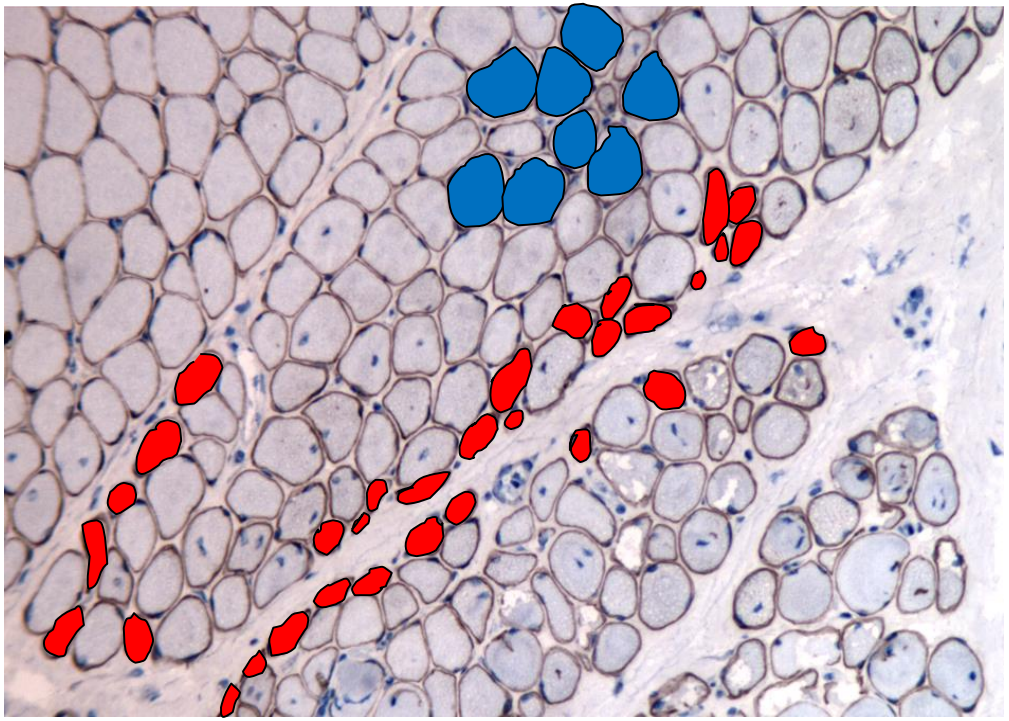
Perifascicular atrophy
and capillary rarefacxtin





Cerbelli et al. Virchows Archiv (2018) 472:477–487





Juvenile Dermatomyositis

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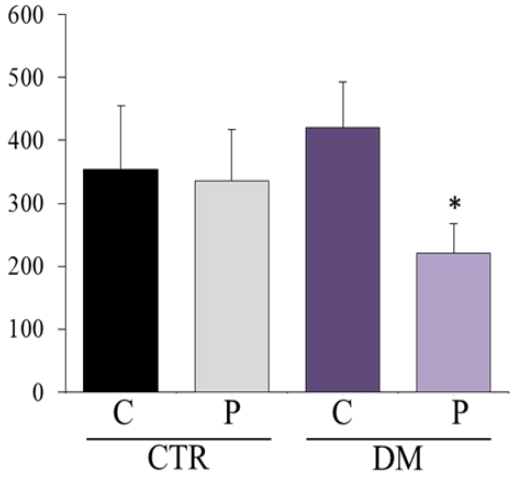

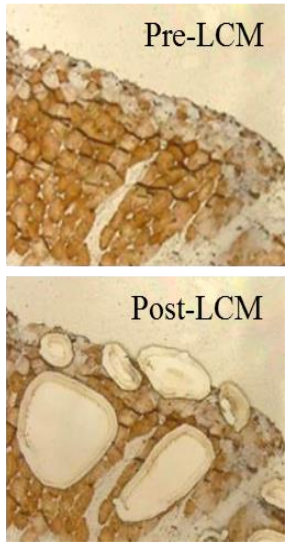

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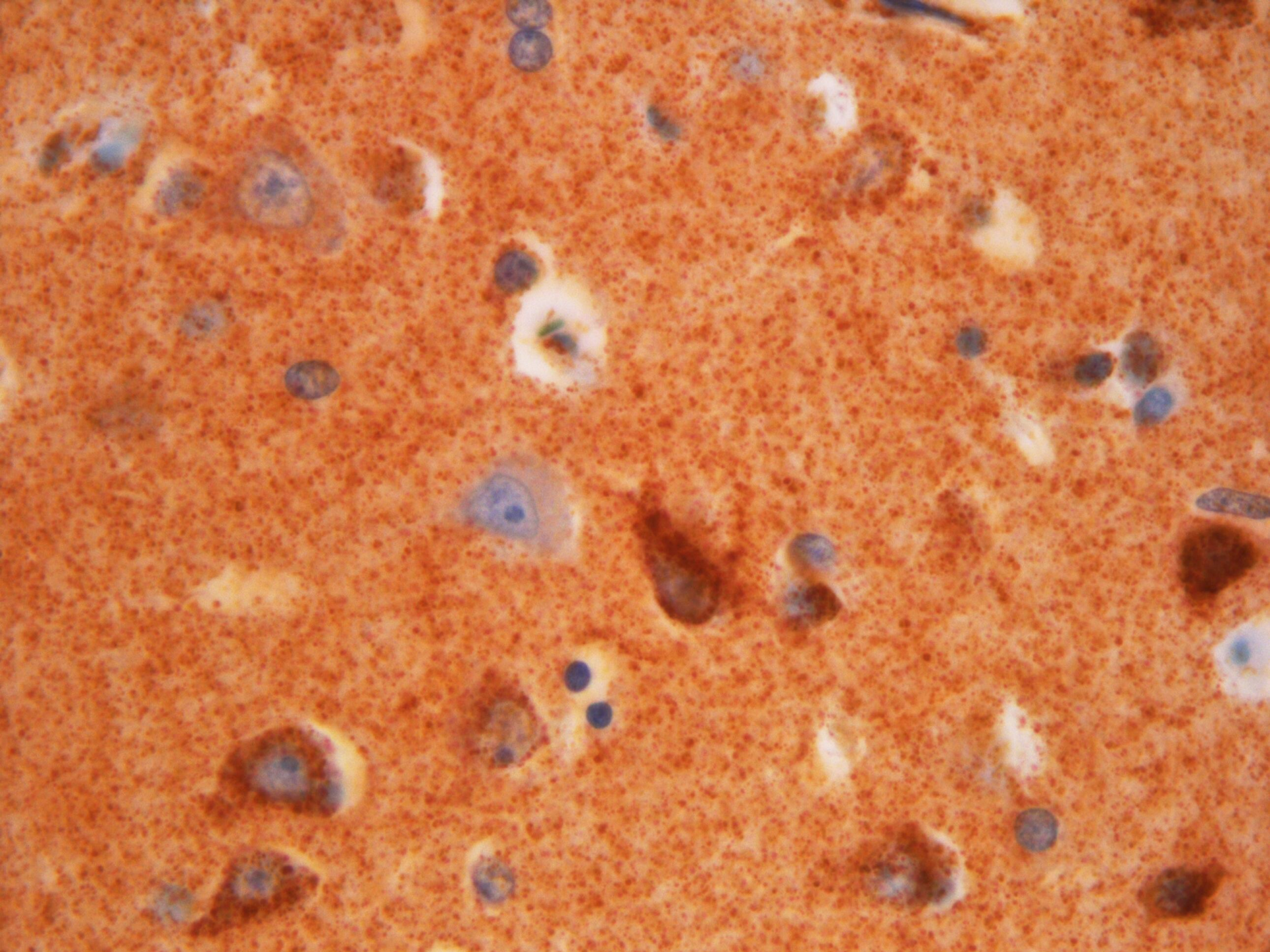

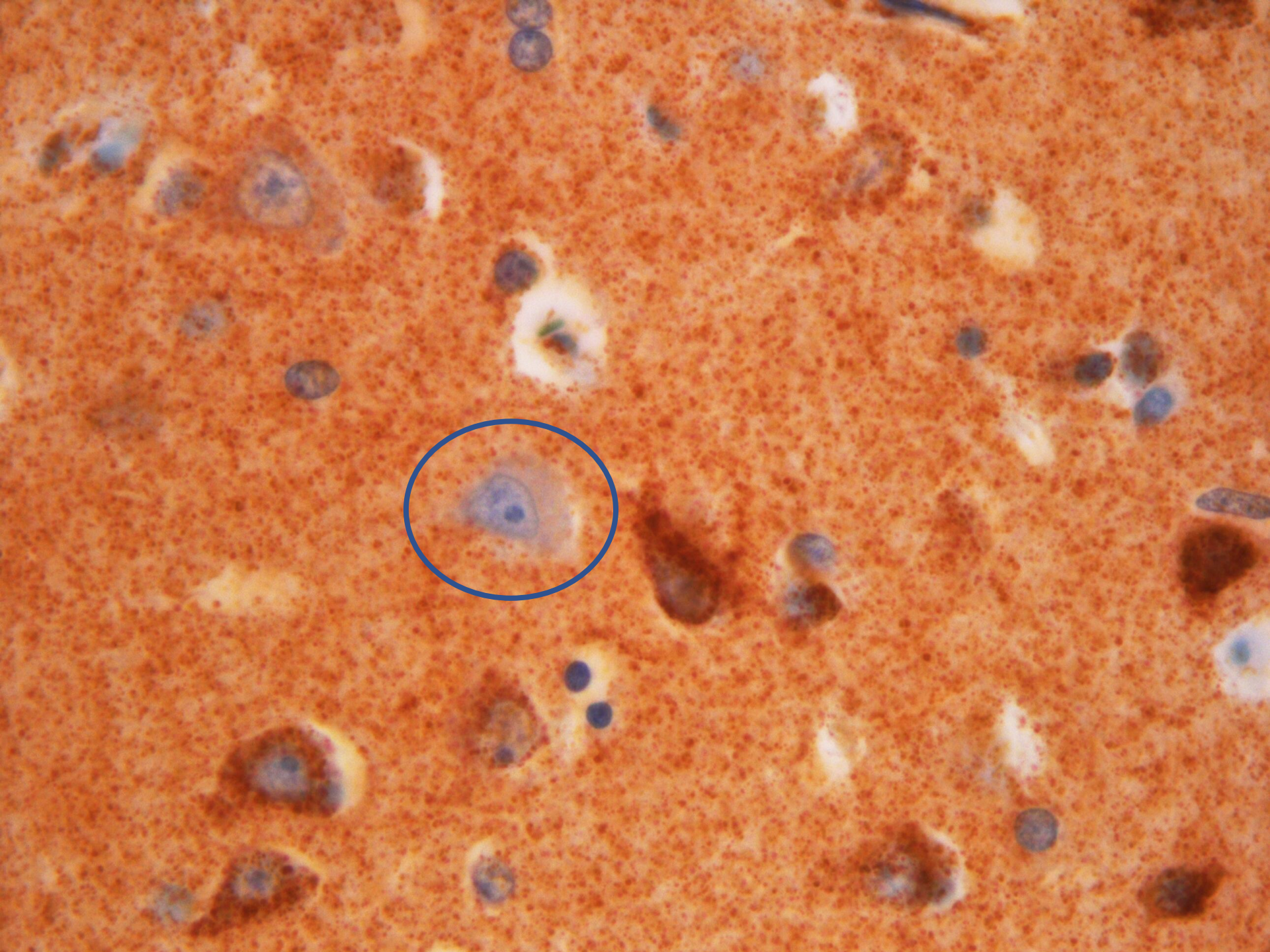

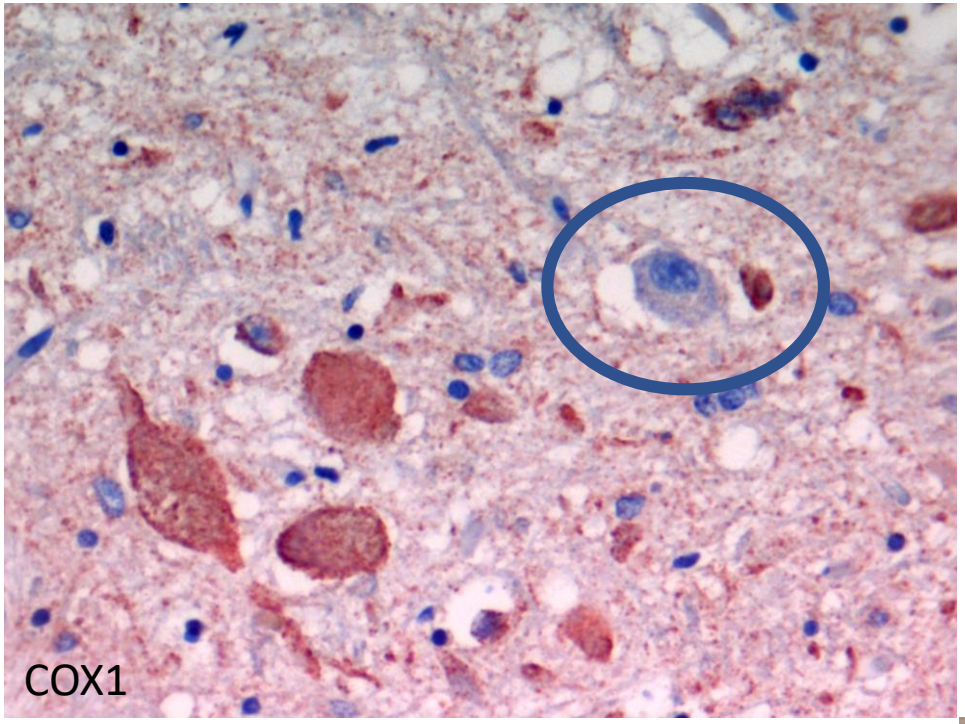
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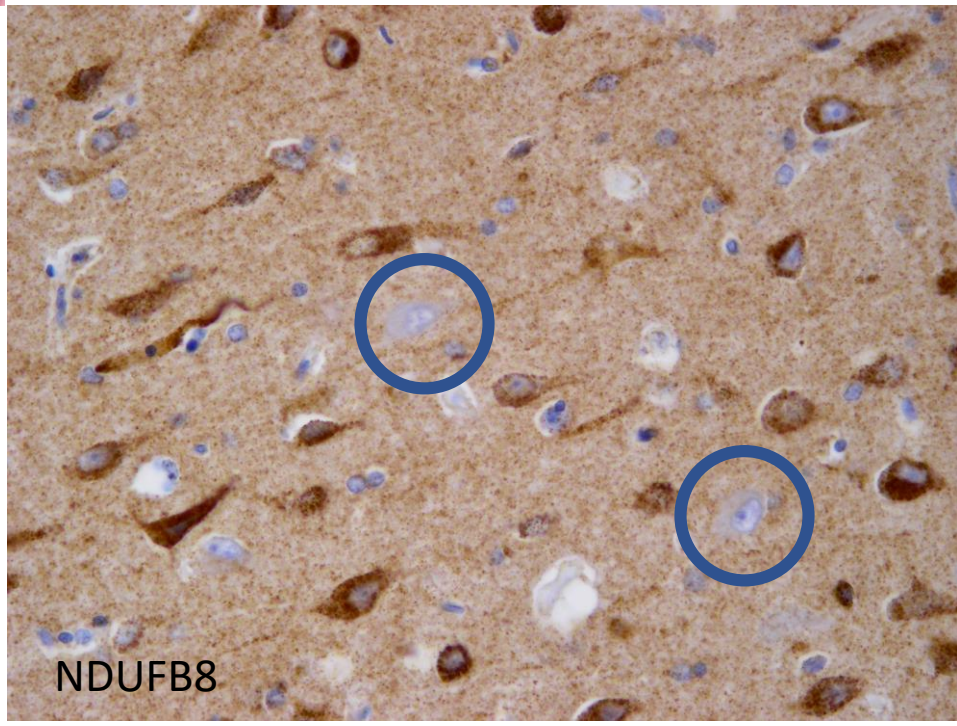
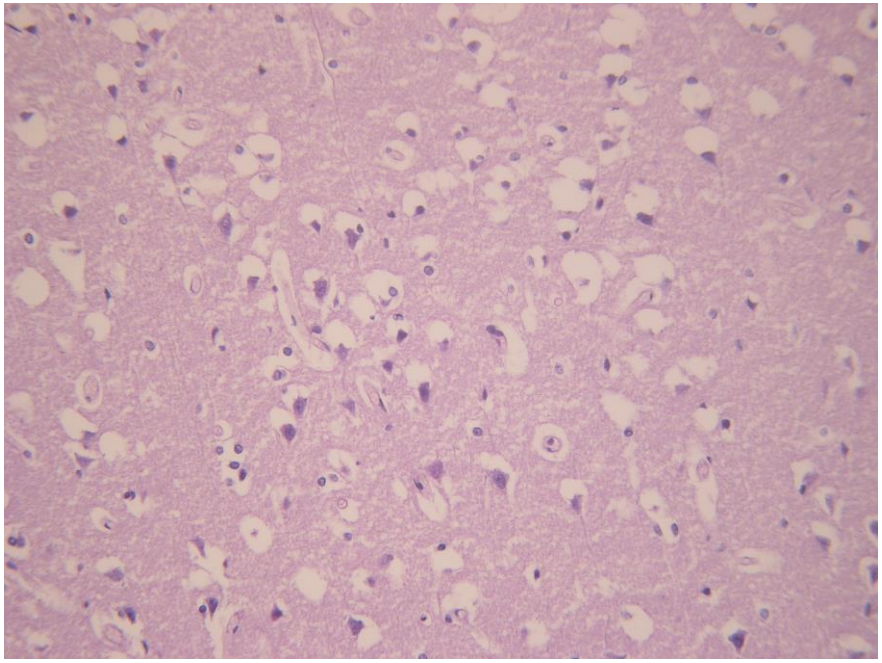
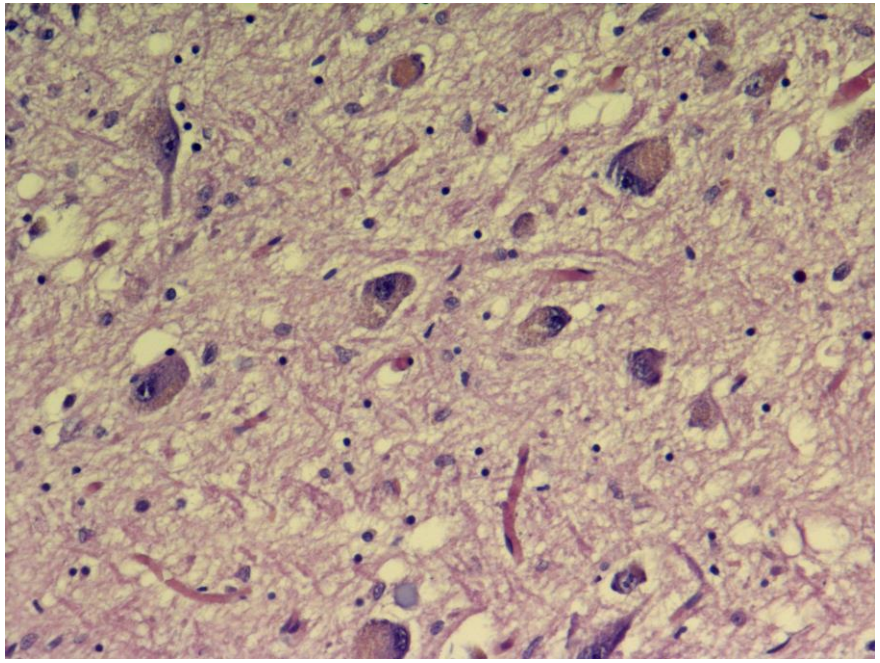

NDUFB8

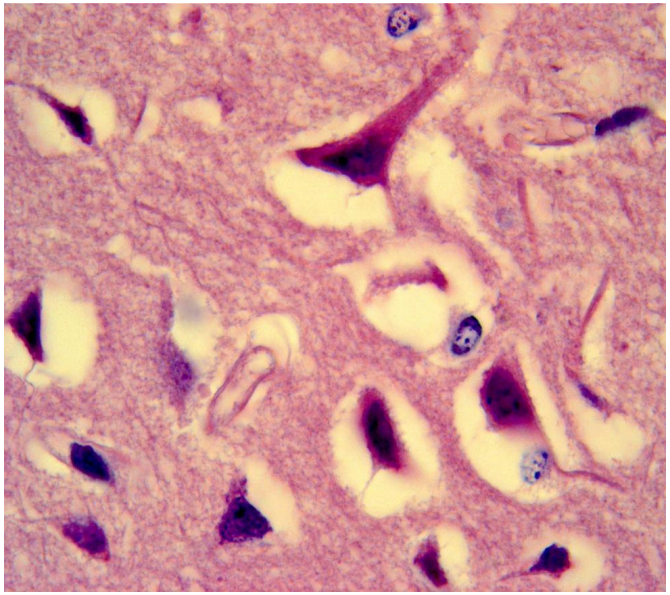
- The histopathological changes that occur in the central nervous system in mitochondrial diseases are *per se* non-specific.

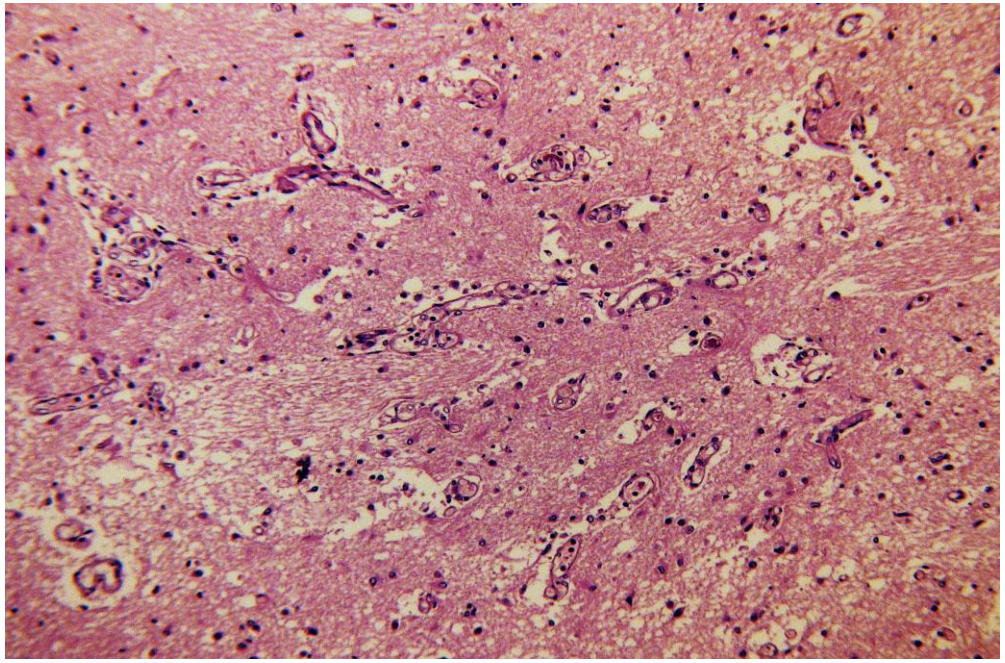
- They can be acute and chronic, can affect both white and gray matter, can affect different regions of the central nervous system, often they do not correlate with the severity of the clinical picture.

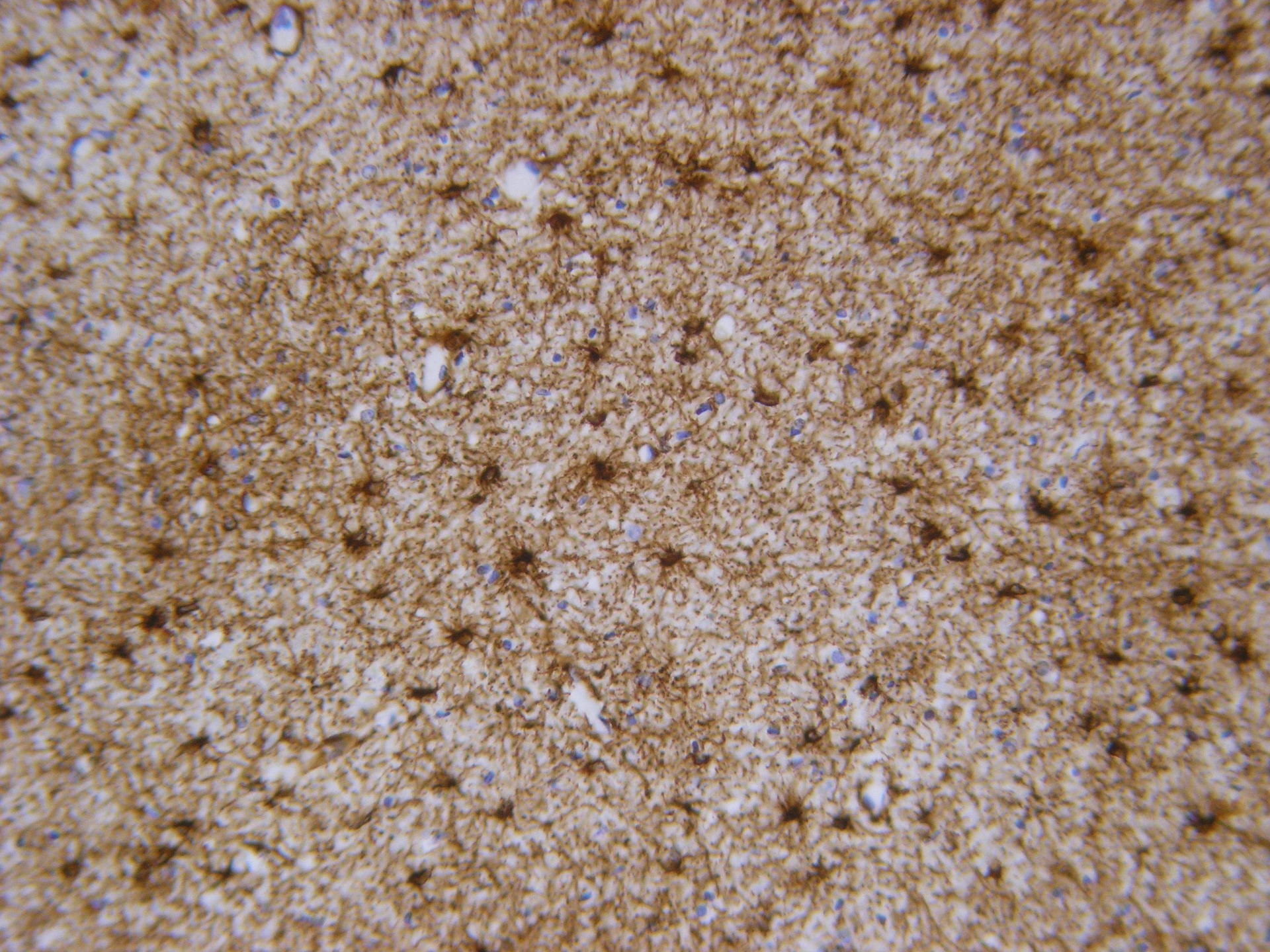
- However, the peculiar distribution of the lesions is often sufficiently characteristic of specific clinical syndromes.

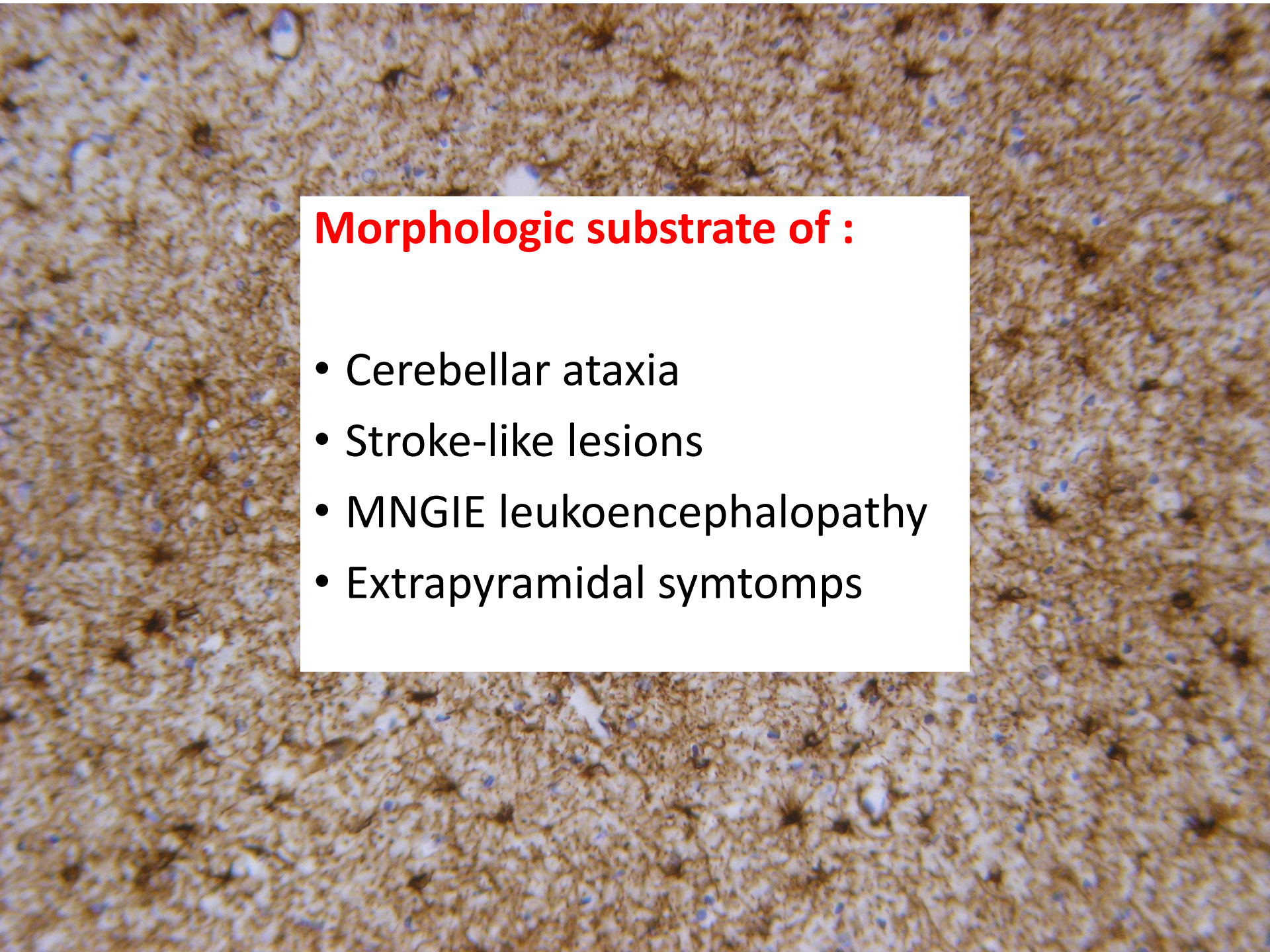








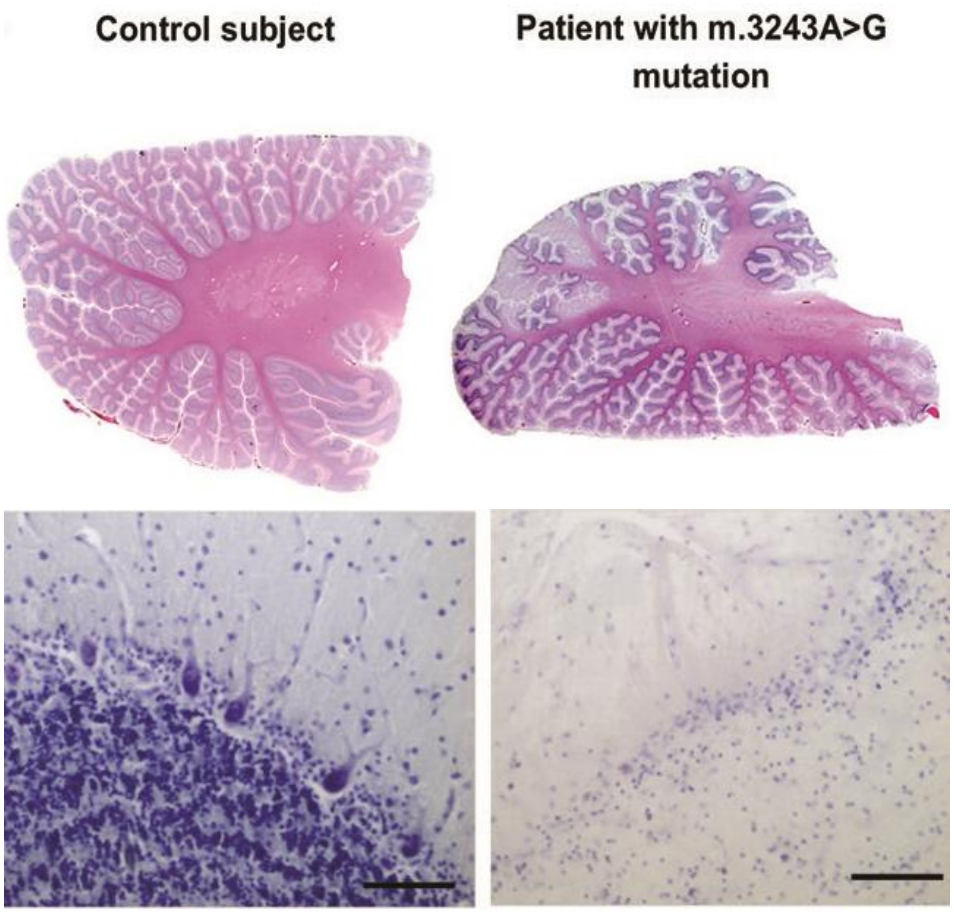




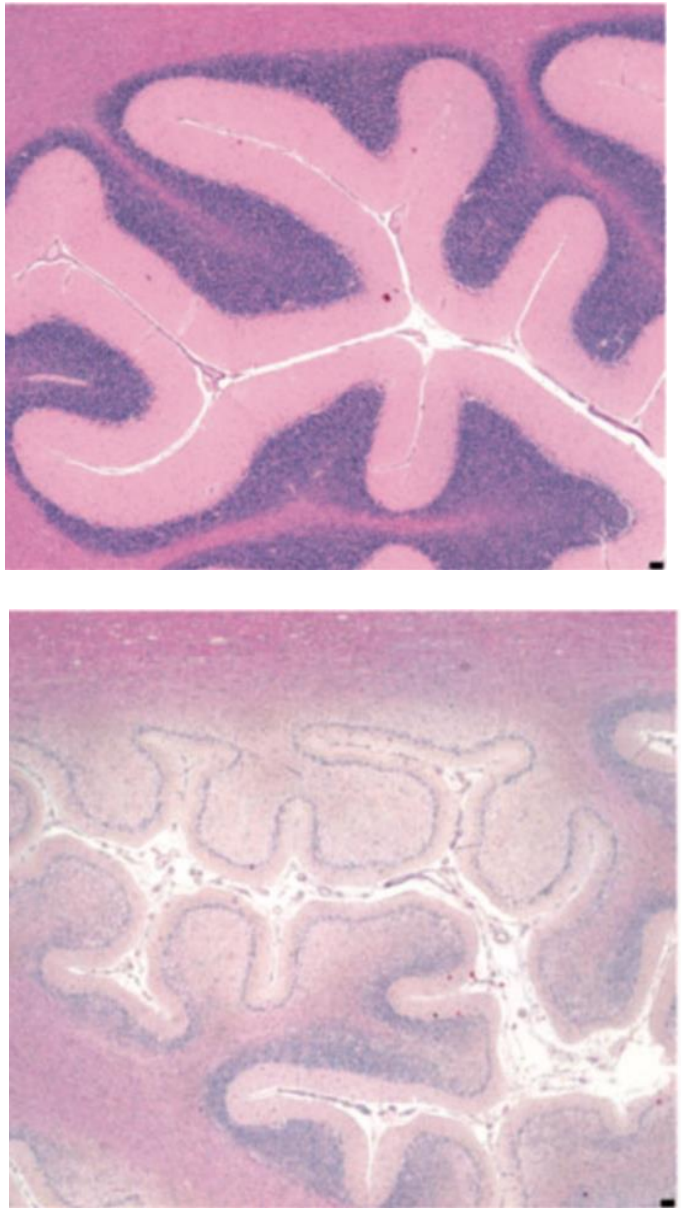
Morphologic substrate of :

- Cerebellar ataxia
- Stroke-like lesions
- MNGIE leukoencephalopathy
- Extrapyramidal symtomps

Morphologic substrate of cerebellar ataxia

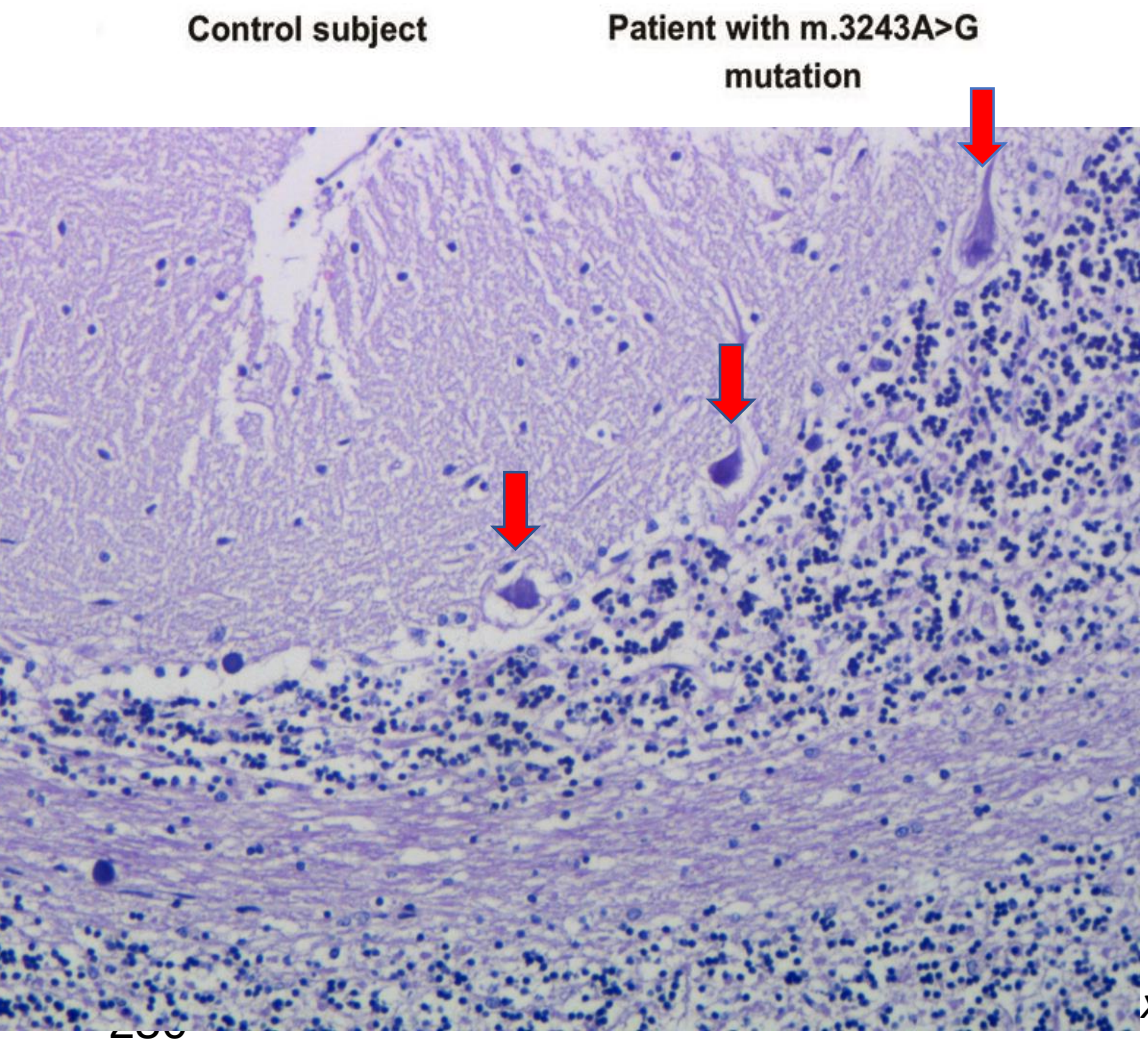


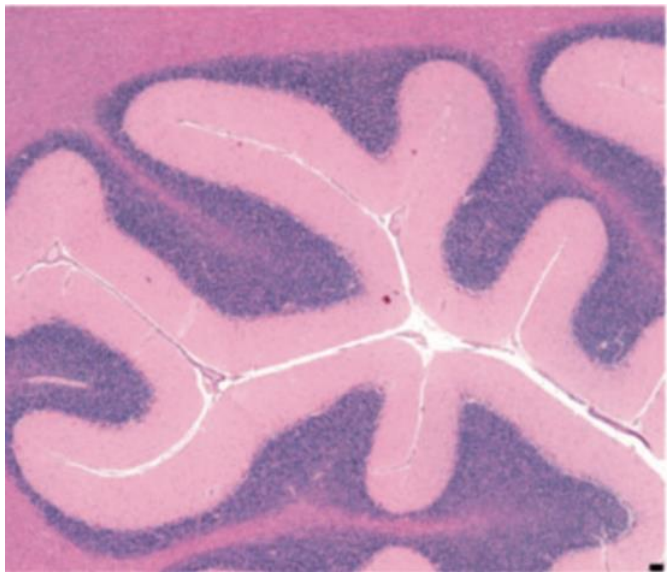
Alston CL et al. J Pathol 2017; **241:** 236–250

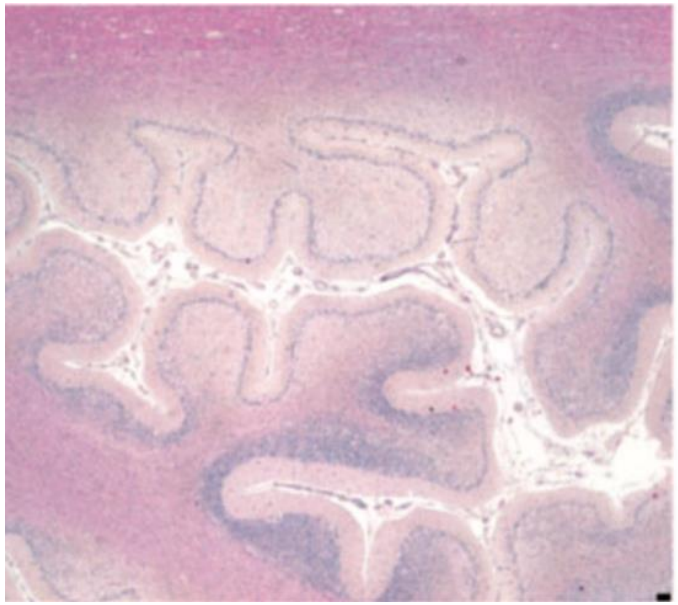


Lax NZ et al. Brain 2012: 135; 1736–1750

Morphologic substrate of cerebellar ataxia



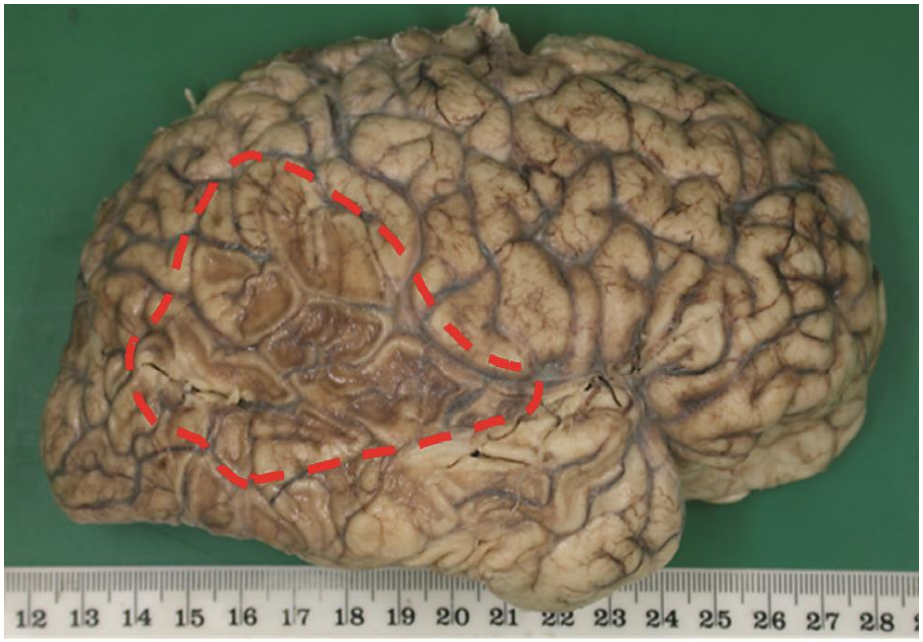




x NZ et al. Brain 2012: 135; 1736–1750

Morphologic substrate of stroke-like lesions

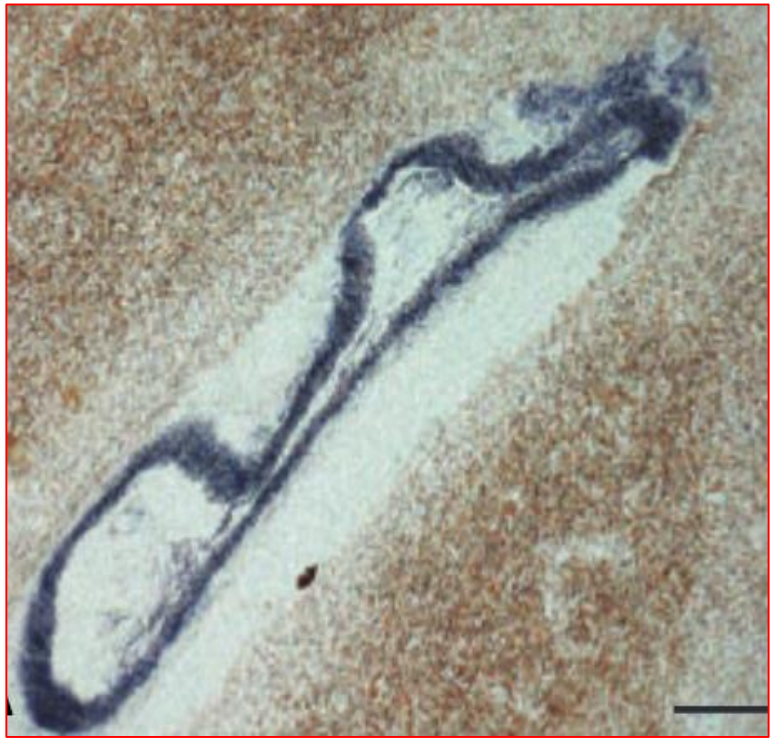
- Multiple foci of neuronal necrosis that do not conform to major vascular territories => focal energy-dependent neuronal necrosis
- They affect the posterior cerebral cortex, basal ganglia and cerebellum of patients bearing MT-TL1 , MT-TK and other mtDNA point mutations, mutations in POLG and FBXL4
- They are ischaemic-like in appearance, exhibiting neuronal cell loss, destruction of the neuropil and subcortical white matter accompanied by proliferation of astrocytes and inflammatory cells.



J Betts *Neuropathology and Applied Neurobiology* (2006), **32**, 359–373

Morphologic substrate of stroke-like lesions

- Mitochondrial angiopathic theory
- Mitochondrial cytopathic theory,
- Neuronal hyperexcitability theory



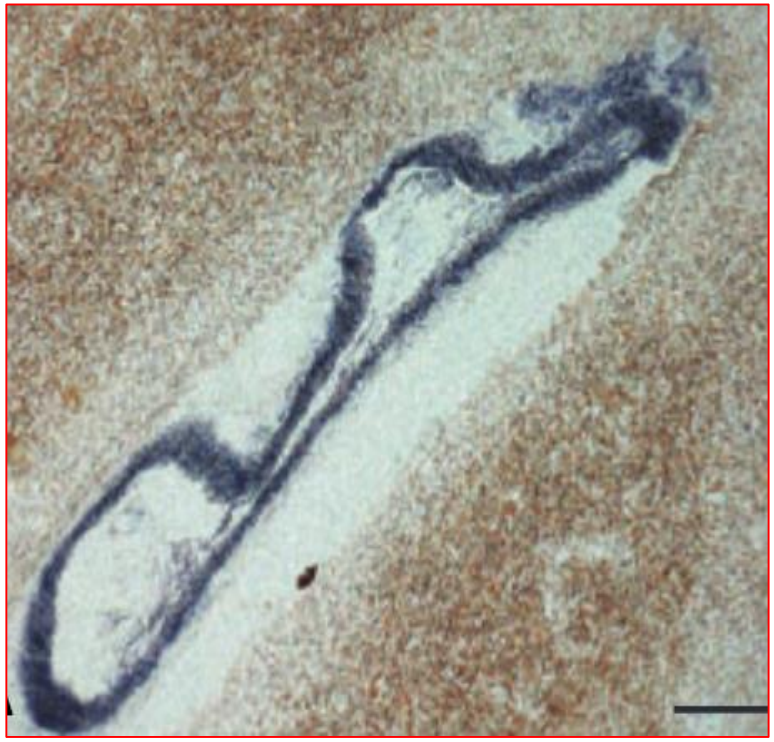
Evidence of strongly SDH reactive microvessels which show accumulation of mitochondria and high mutant load. Plasma protein extravasation following fibrinogen and IgG immunohistochemistry suggest that vessels damage might compromise cerebrovascular autoregulation and therefore blood vessel tone.

→ **BBB break-down**

Morphologic substrate of stroke-like lesions

Microangiopathy in the cerebellum of patients with mitochondrial DNA disease

Lax NZ et al. Brain 2012: 135; 1736–1750



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→ **BBB break-down**

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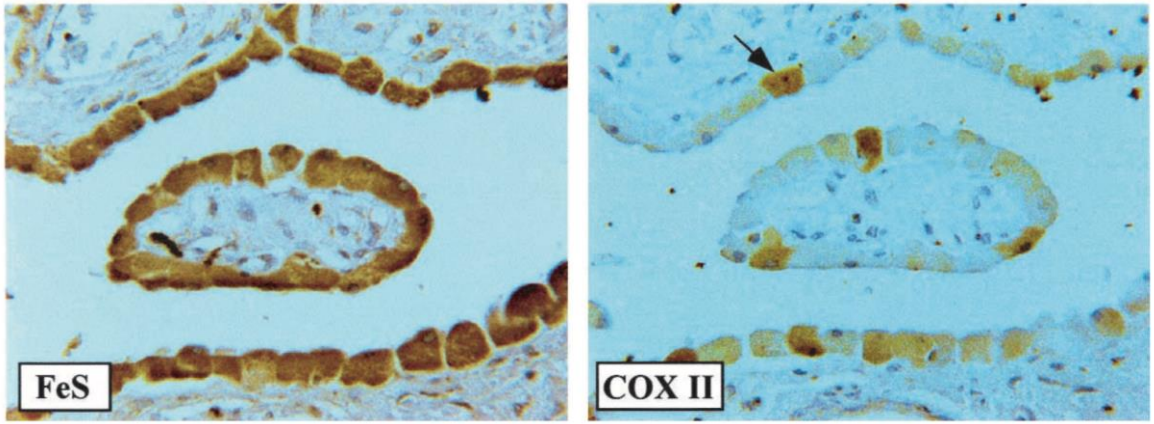
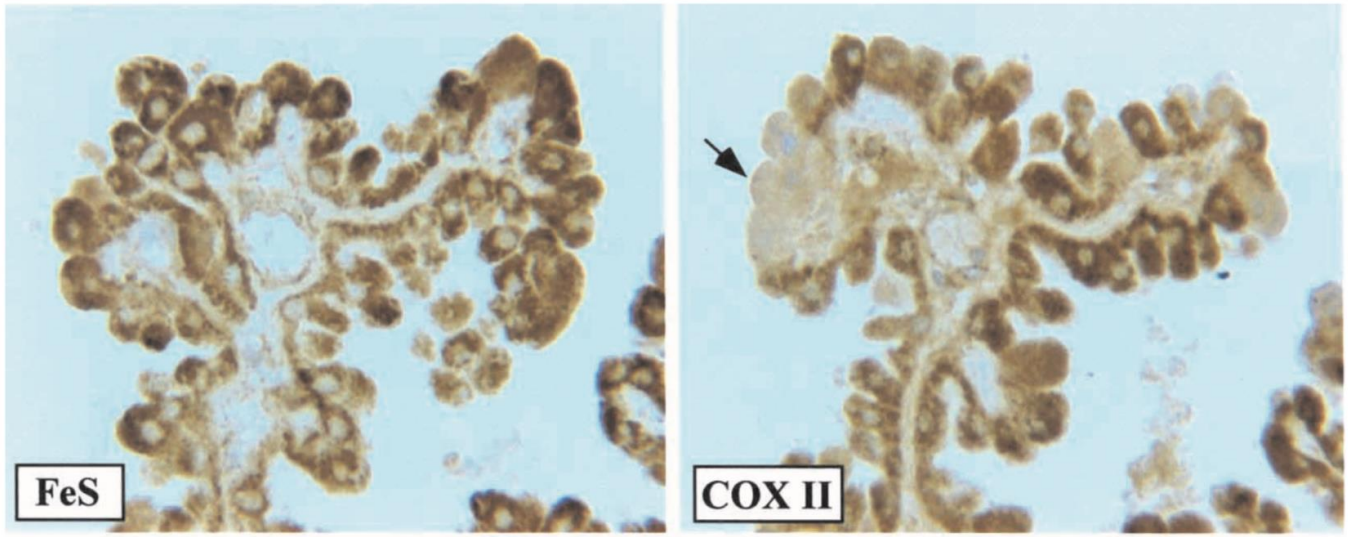
doi:10.1006/scdb.2001.0280, available online at http://www.idealibrary.com on IDEAL®

Neuropathological features of mitochondrial disorders

*Kurenai Tanji, Teruhito Kunimatsu, Tuan H. Vu and Eduardo Bonilla**



KSS

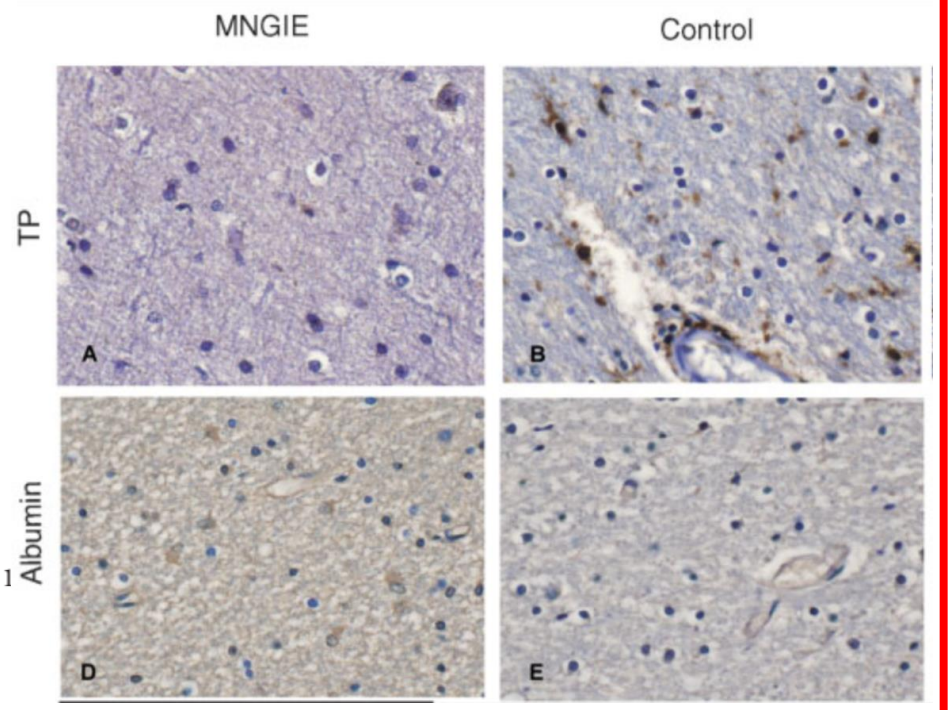


MELAS

Morphologic substrate of leukoencephalopathy in MNGIE

Increased Blood–Brain Barrier Permeability with Thymidine Phosphorylase Deficiency

Kinga Szigeti, MD,[1] Norbert Sule, MD,[2]
Adekunle M. Adesina, MD, PhD,[2]
Dawna L. Armstrong, MD,[2] Gulam M. Saifi, PhD,[1]
Eduardo Bonilla,[3] Michio Hirano, MD,[3]
and James R. Lupski, MD, PhD[1,4]

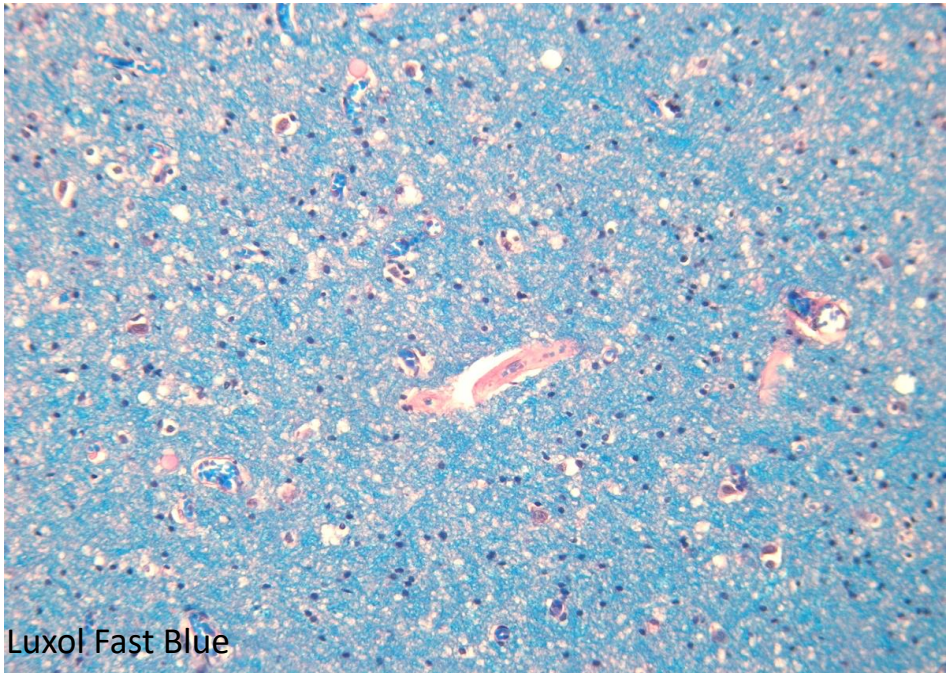


Cerebral Mitochondrial Microangiopathy Leads to Leukoencephalopathy in Mitochondrial Neurogastrointestinal Encephalopathy

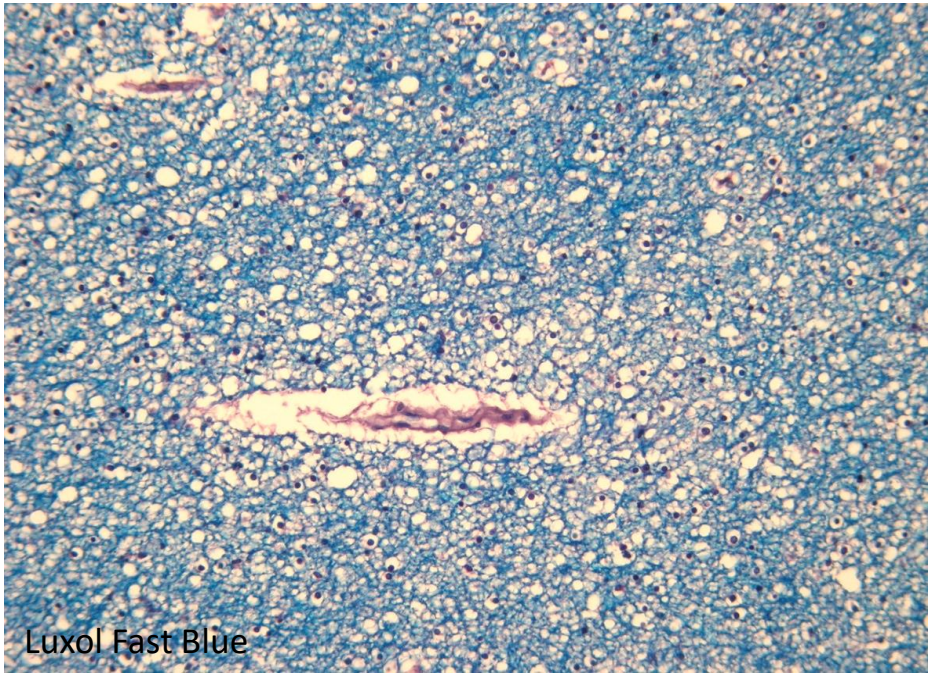
L.L. Gramegna, A. Pisano, C. Testa, D.N. Manners, R. D'Angelo, E. Boschetti, F. Giancola, L. Pironi, L. Caporali, M. Capristo, M.L. Valentino, G. Plazzi, C. Casali, M.T. Dotti, G. Cenacchi, M. Hirano, C. Giordano, P. Parchi, R. Rinaldi, R. De Giorgio, R. Lodi, V. Carelli, and C. Tonon

AJNR Am J Neuroradiol 39:427–34 Mar 201

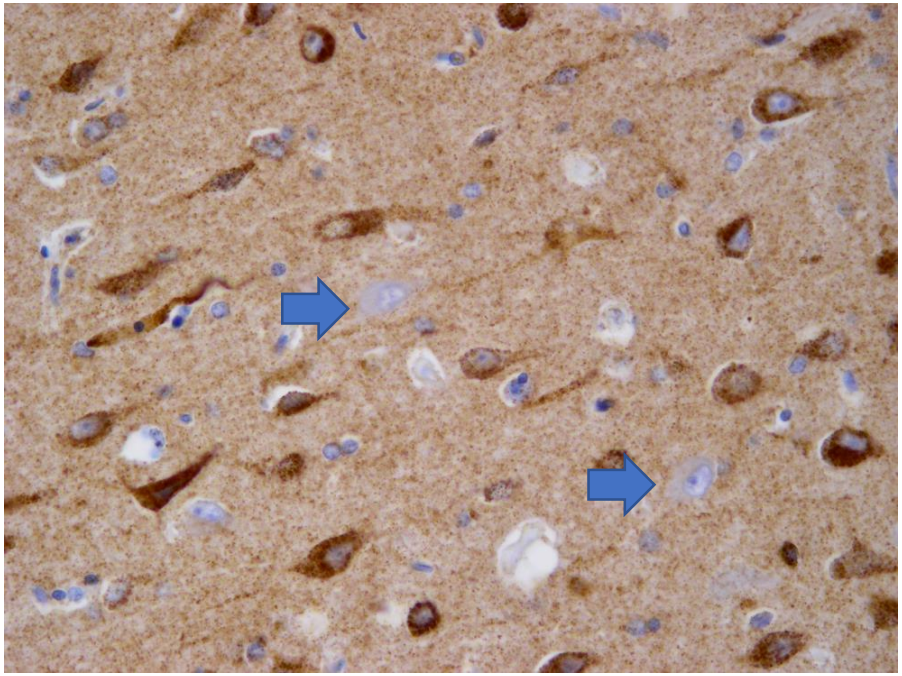
Control

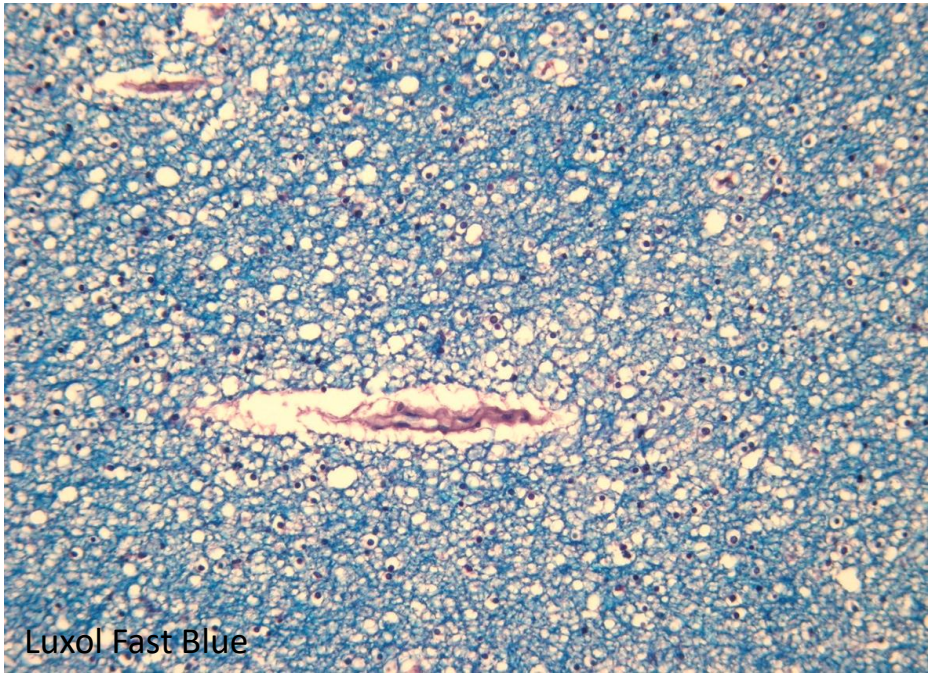


MNGIE

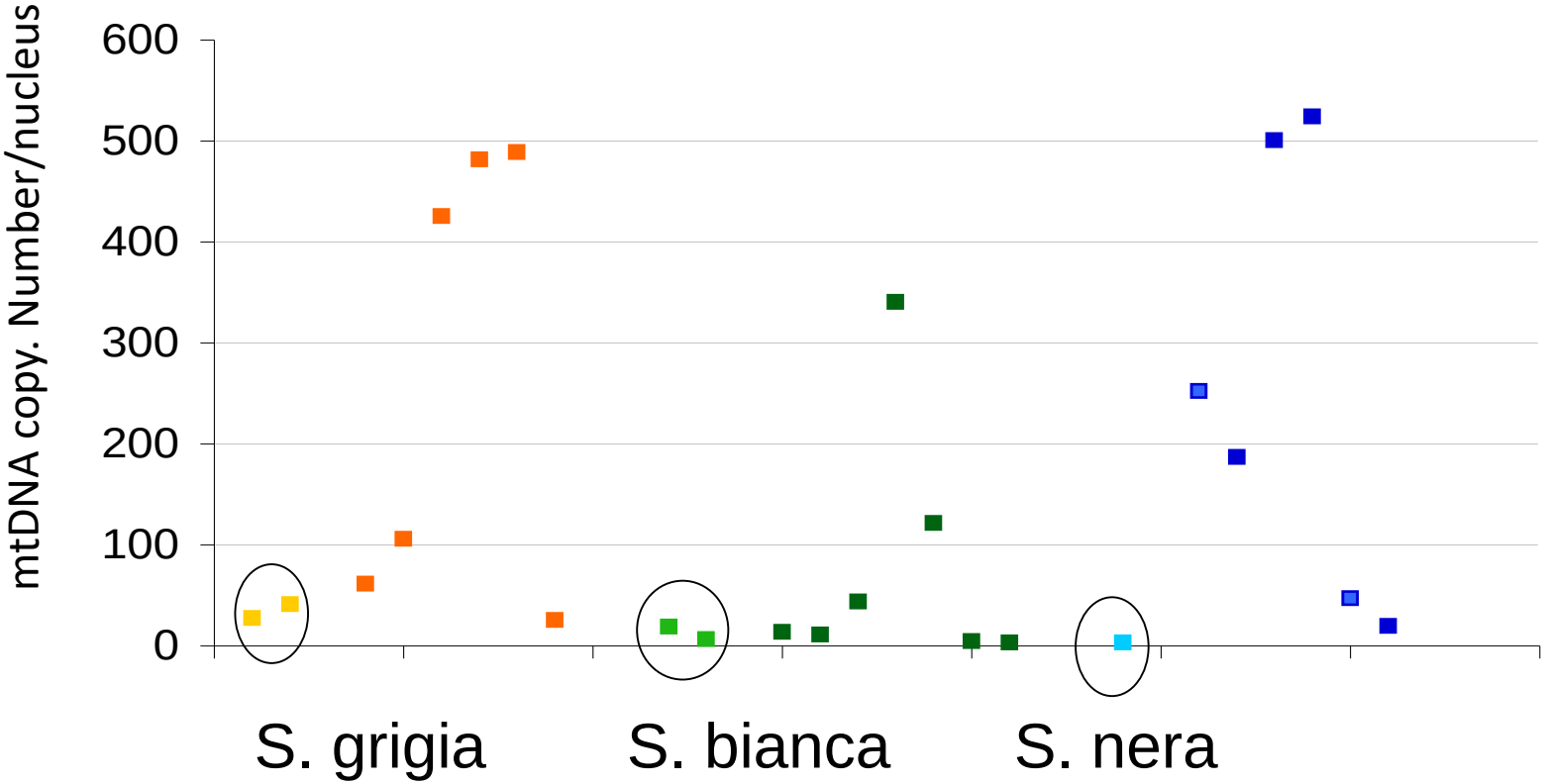


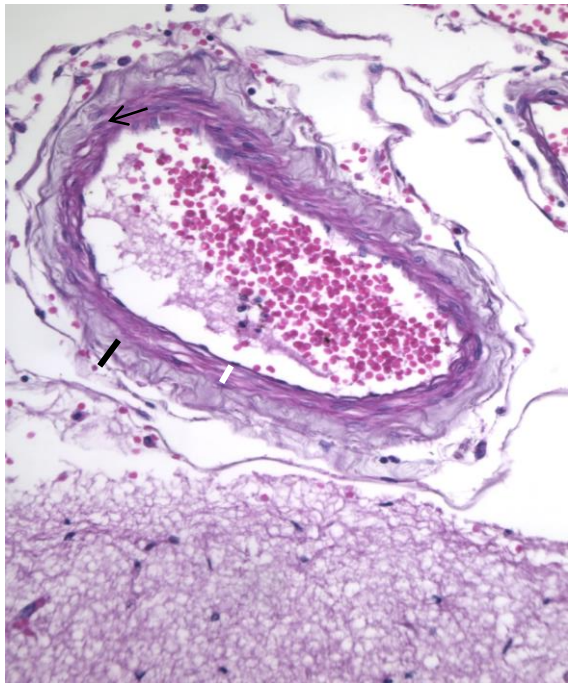
MNGIE

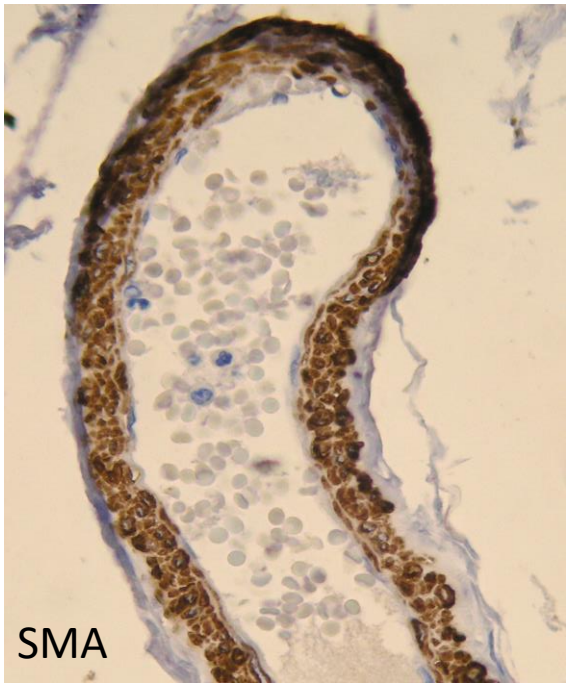


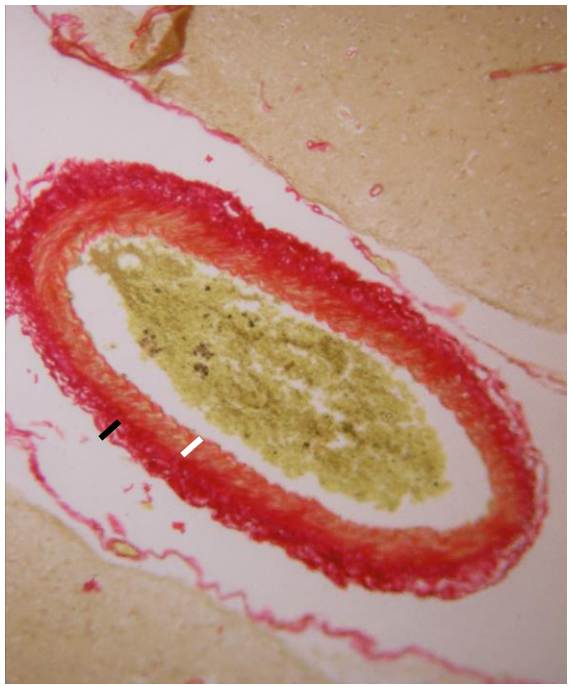


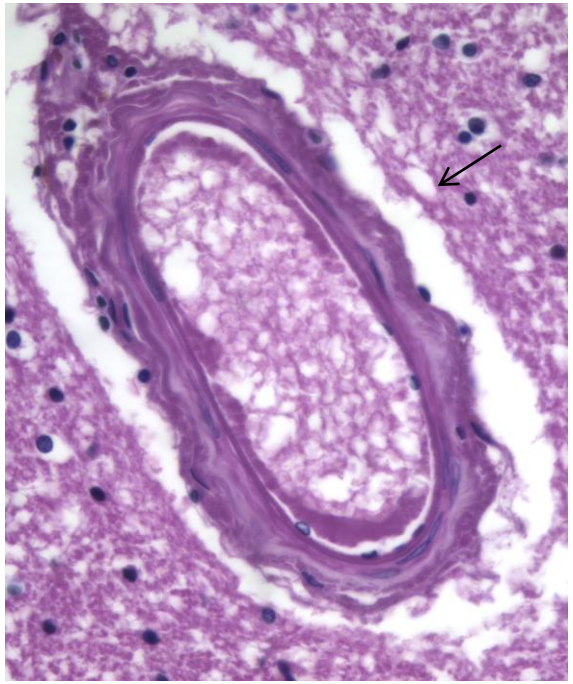
Evaluation of mtDNA copy number in different regions of MNGIE brain by LCM

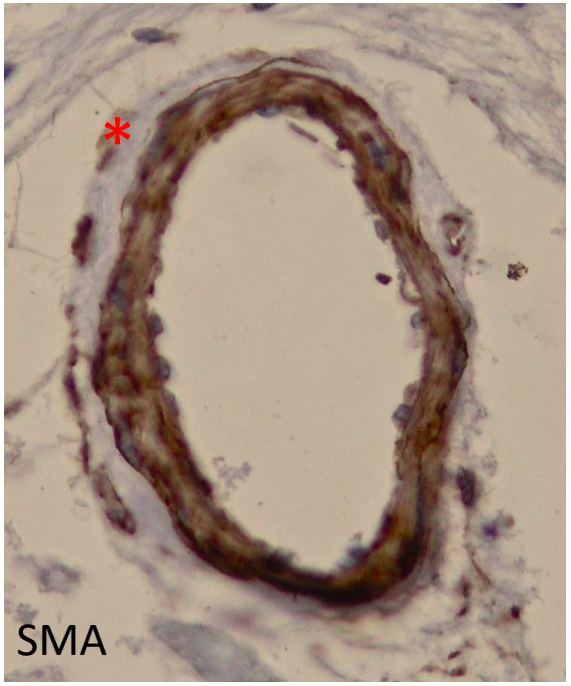





SMA



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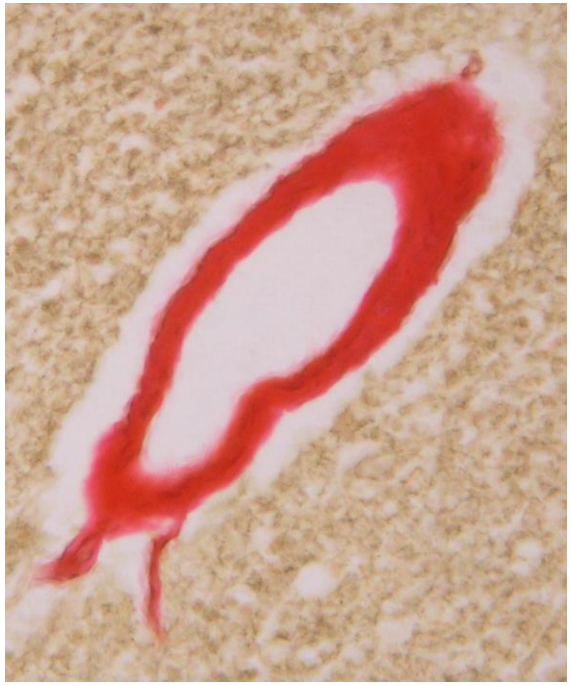
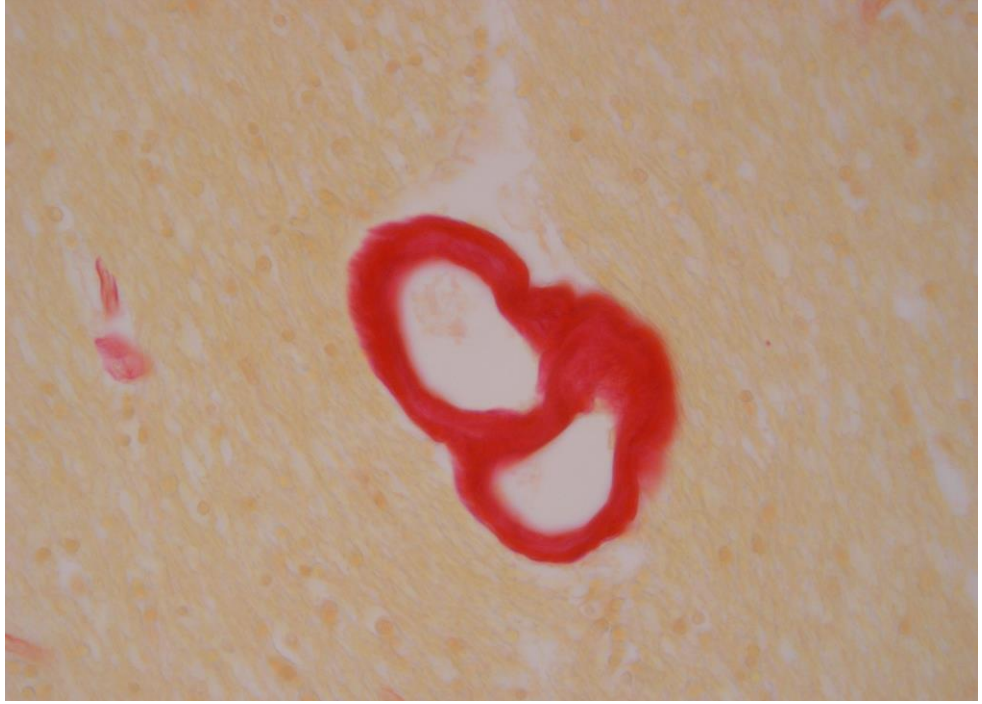
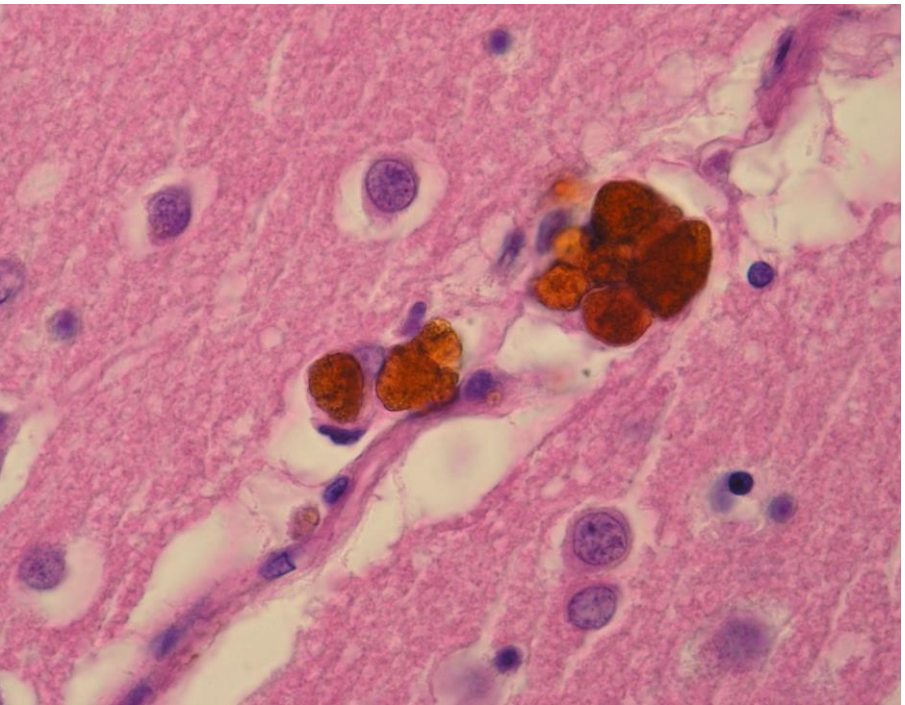
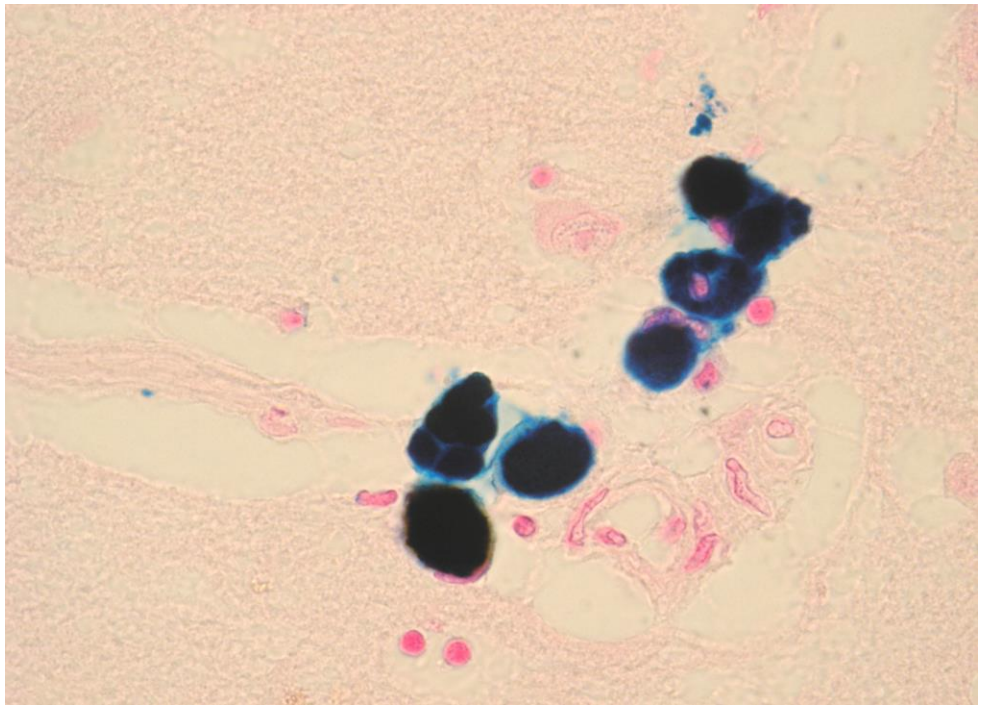


- Diffuse replacement of the vascular wall by dense fibrous tissue and multiple perivascular microbleeds in the white matter of the frontal lobe, in the basal ganglia, and in the midbrain.







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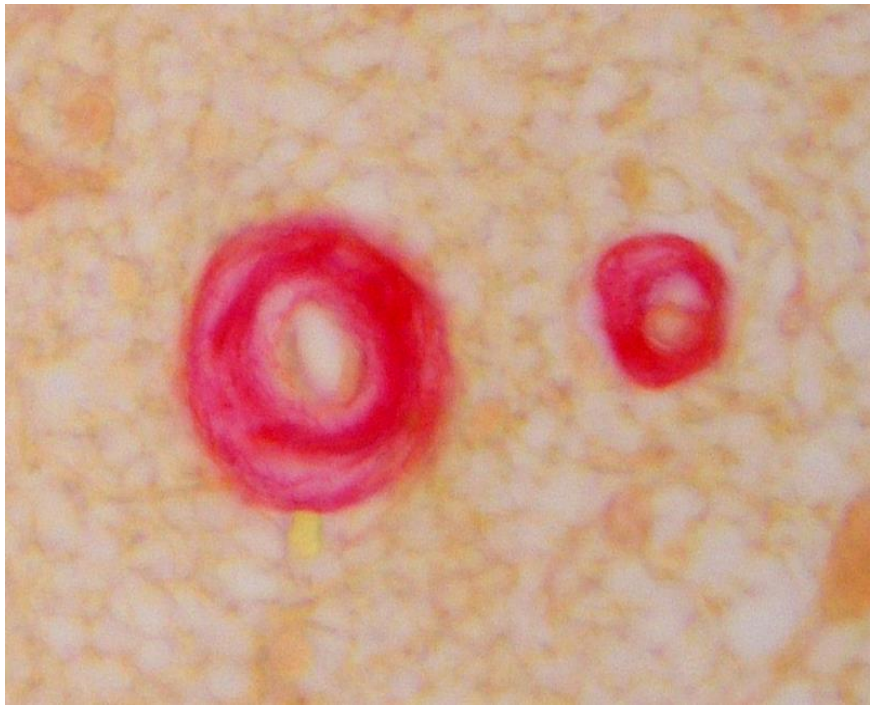
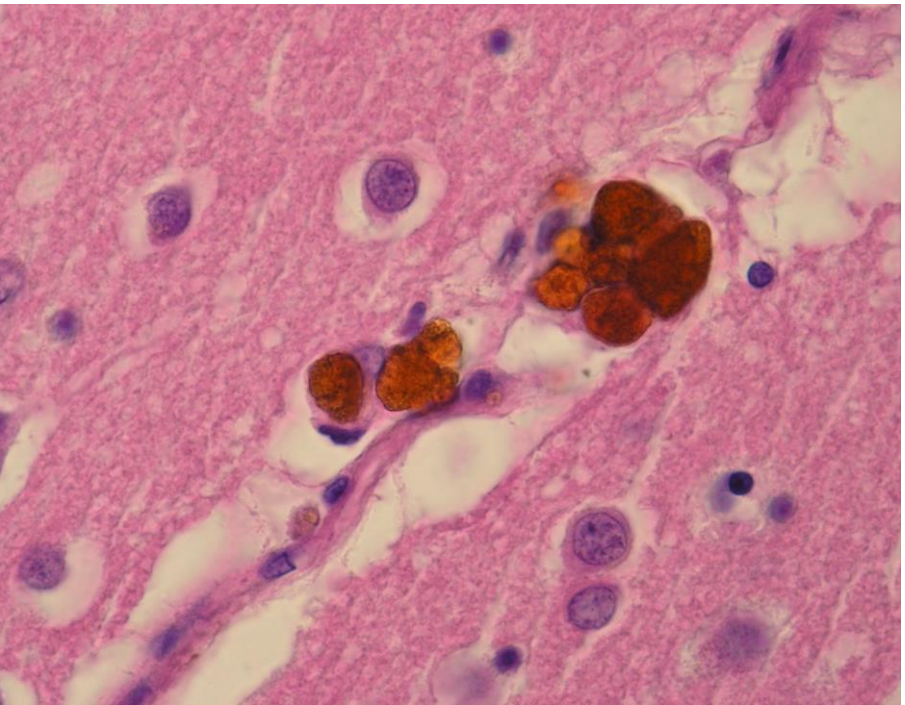
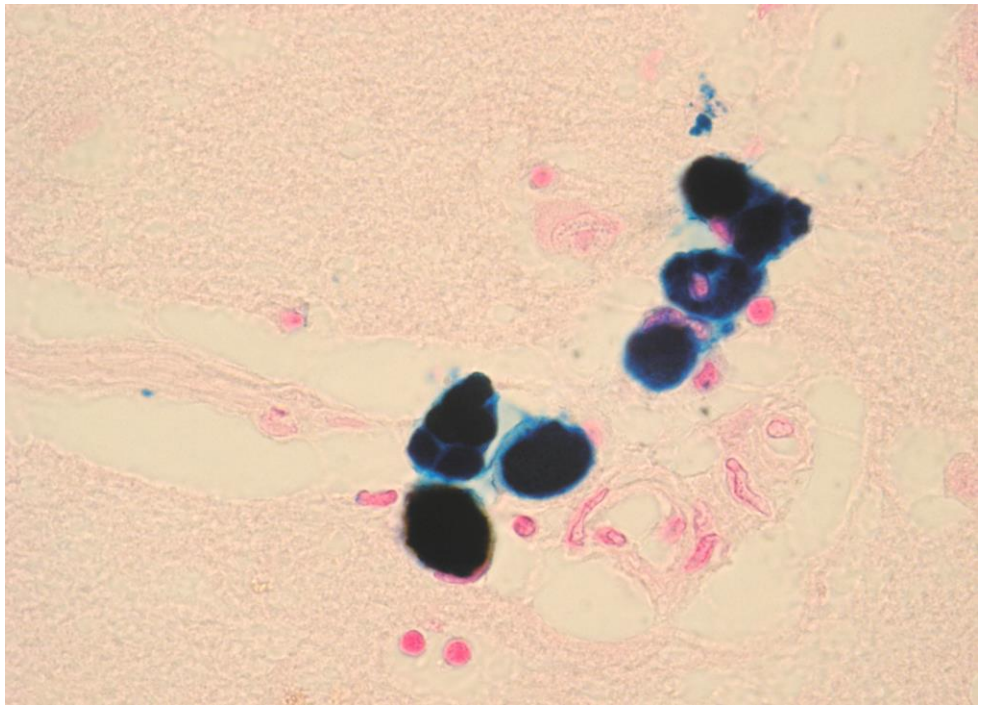
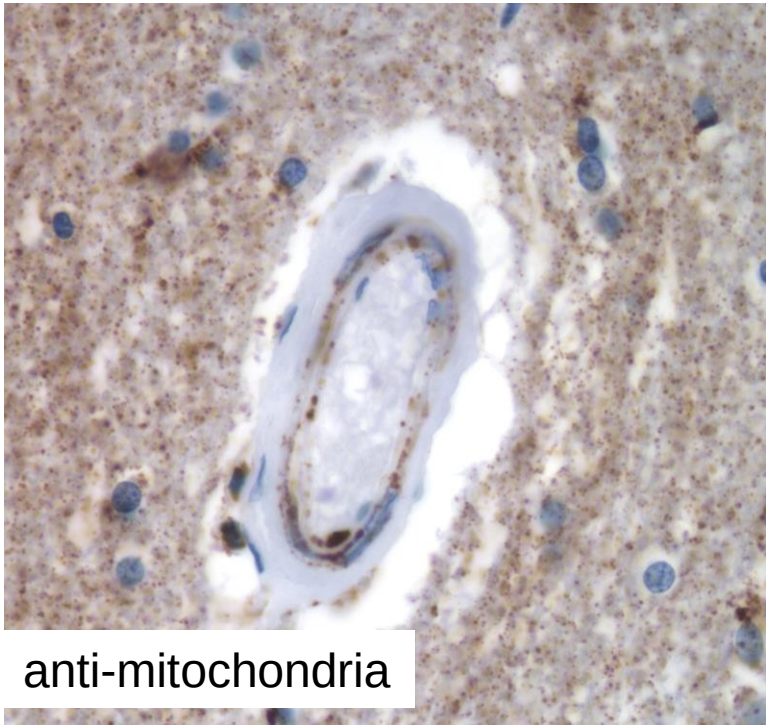
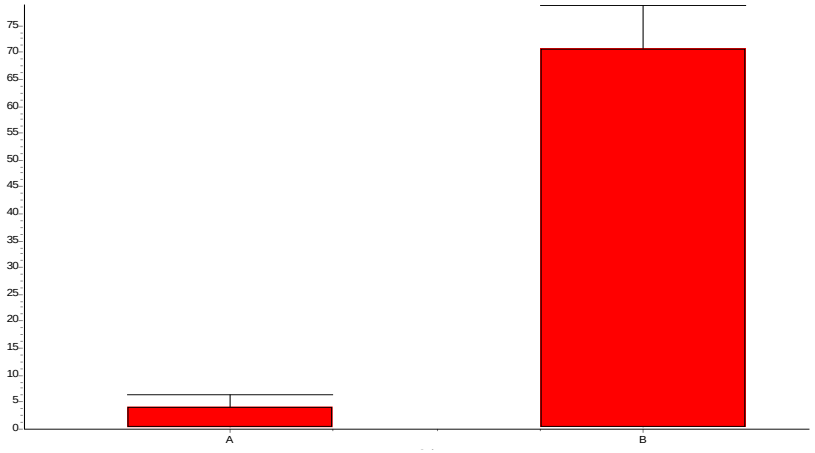


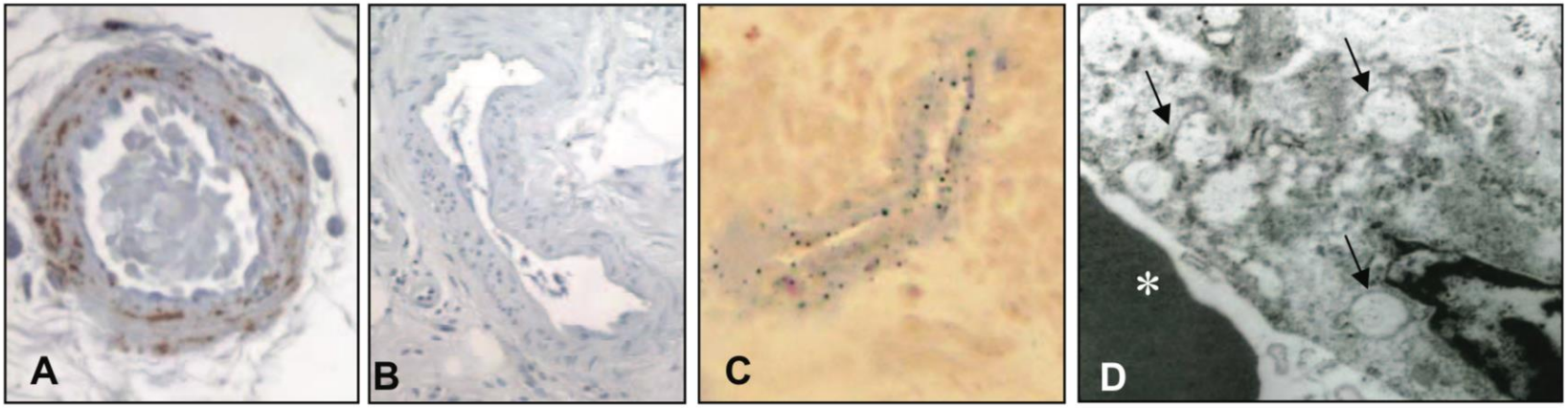






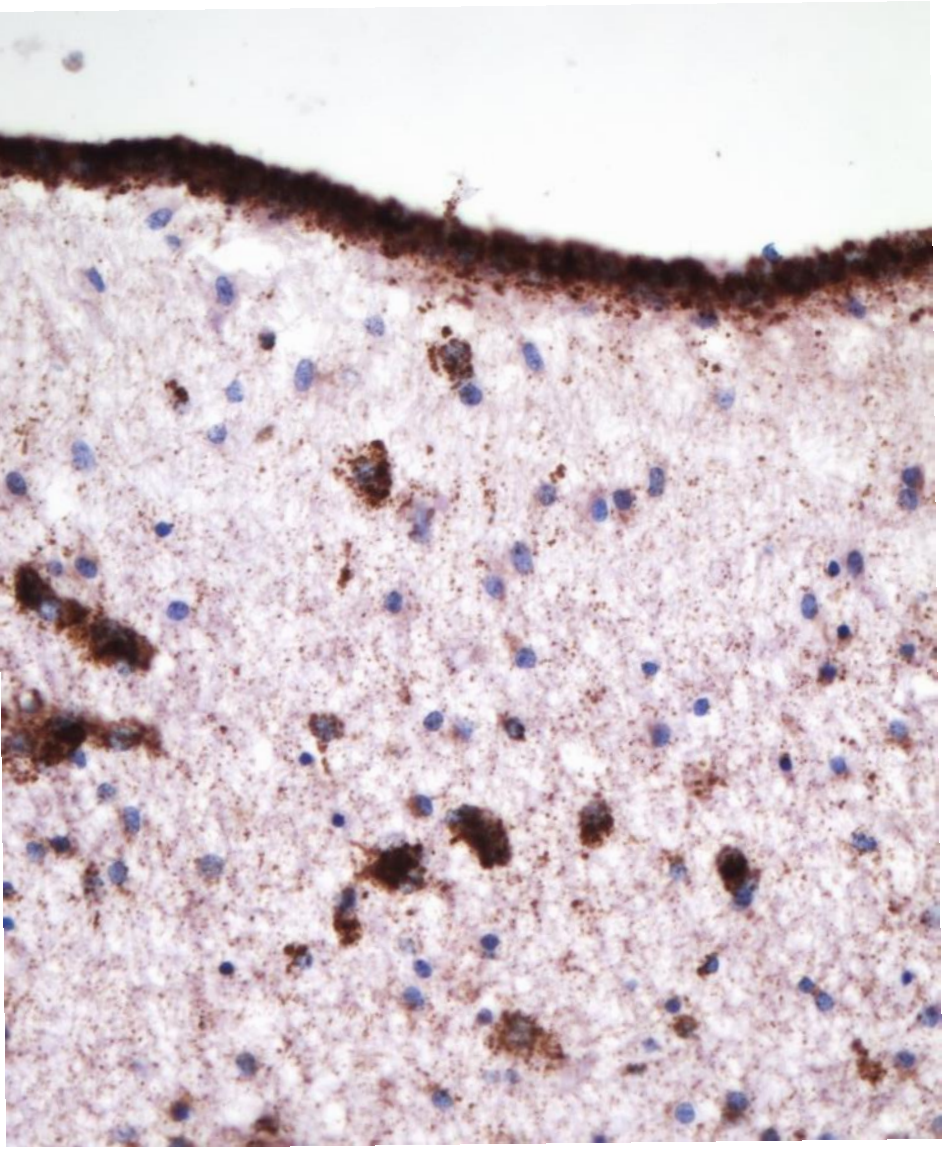
mtDNA copynumber/ cell in vessels from MNGIE brain



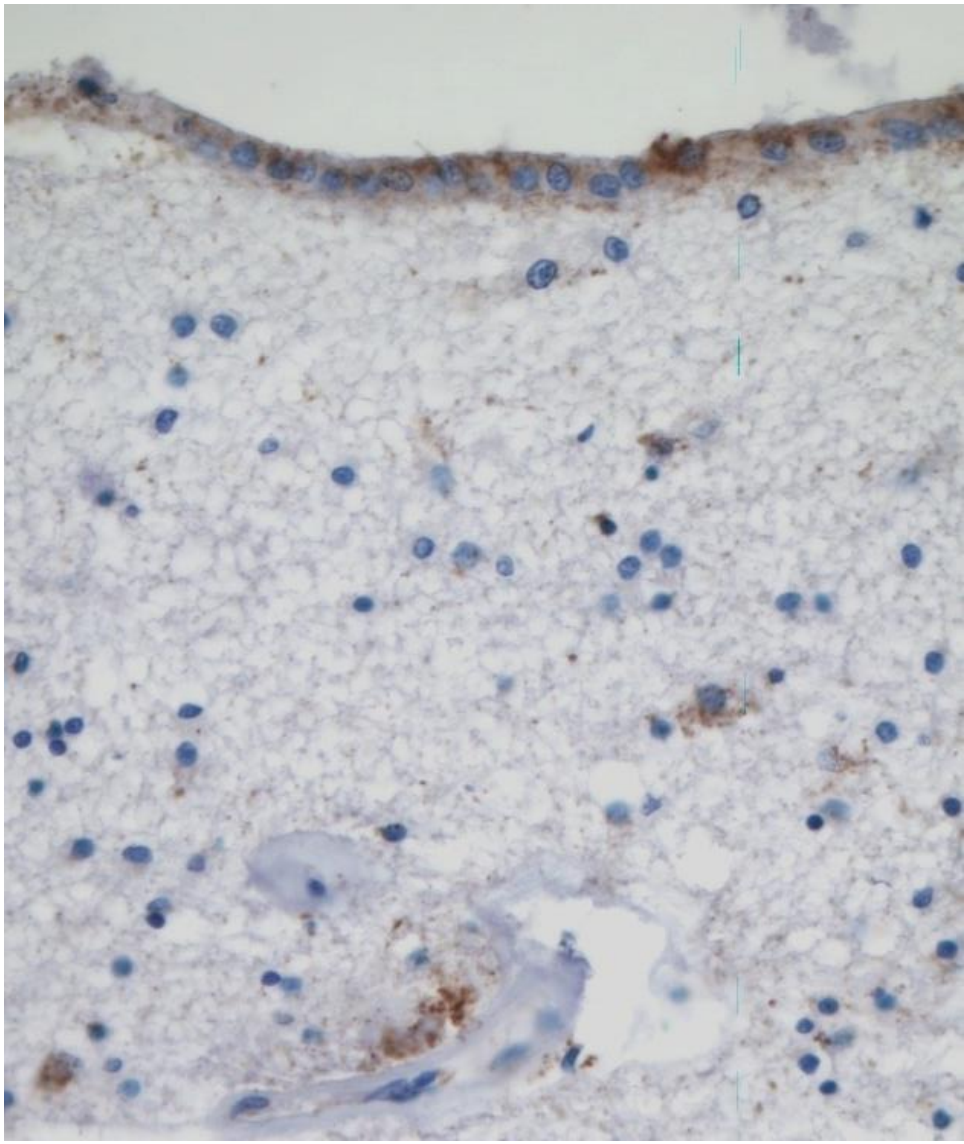


Giordano C et al. **Gastrointestinal dysmotility in mitochondrial neurogastrointestinal encephalomyopa-thy is caused by mitochondrial DNA depletion.** *Am J Pathol* 2008; 173:1120 –28

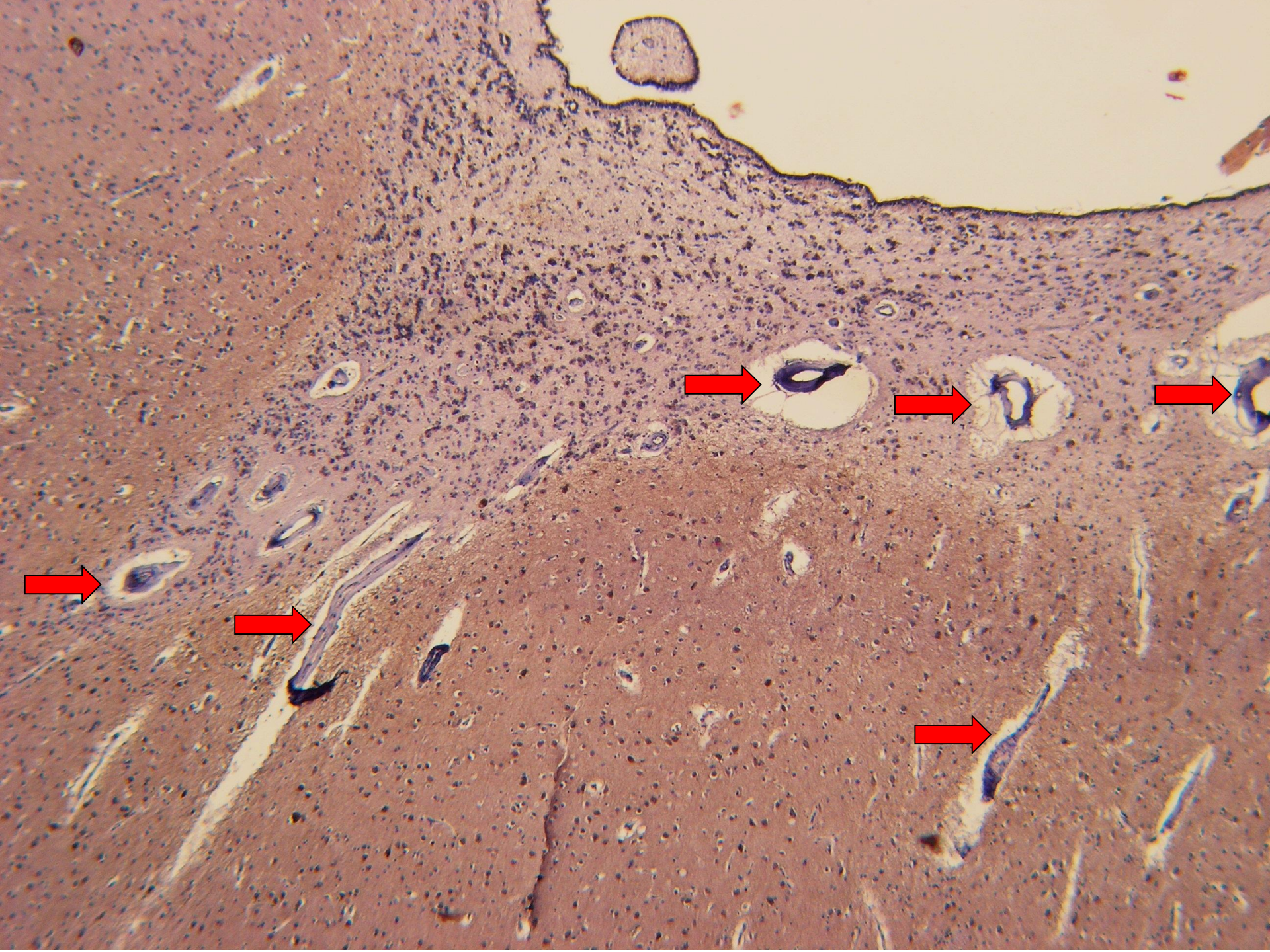
- COX deficiency in the periependymal tissue



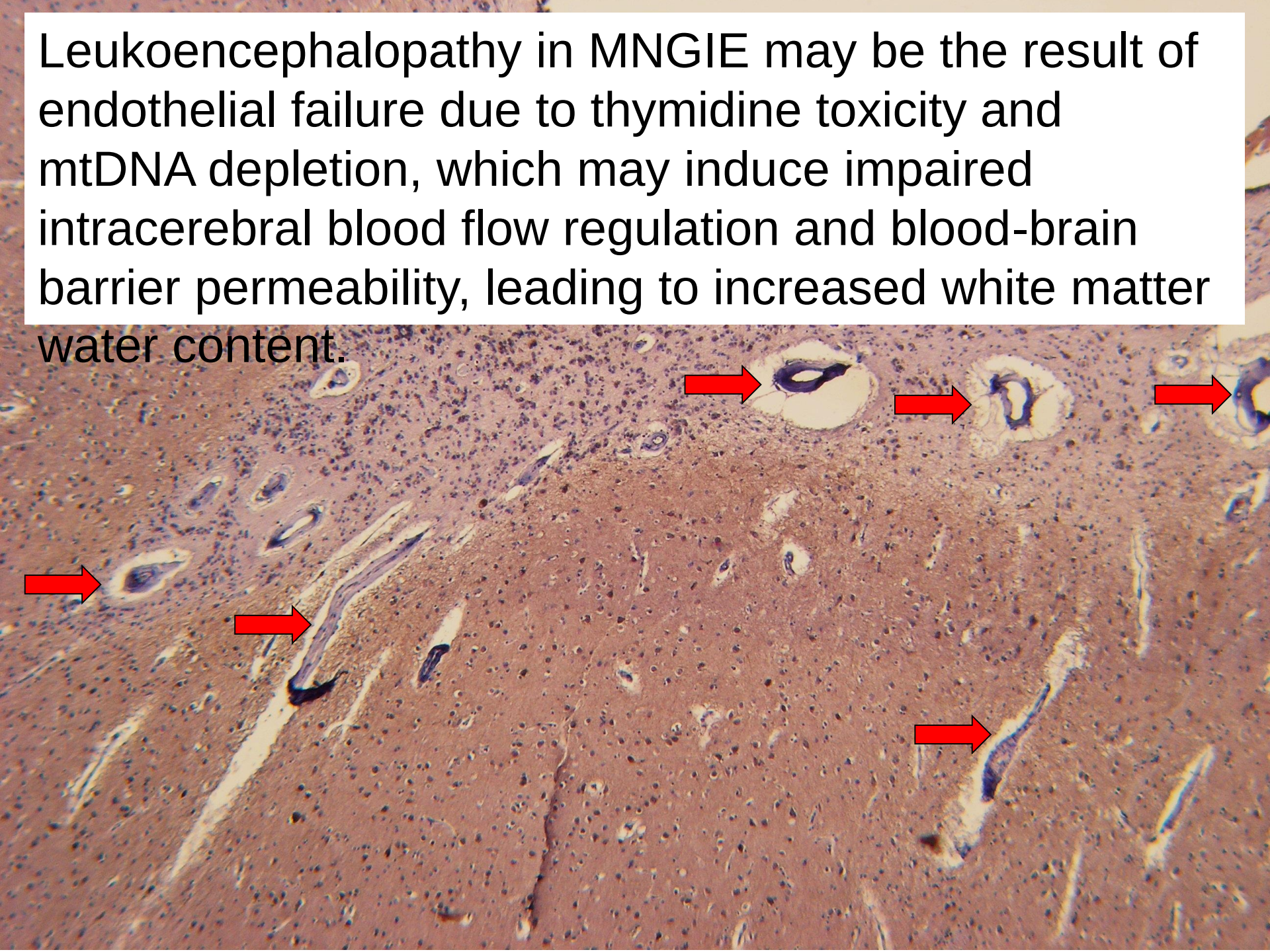
COXIV



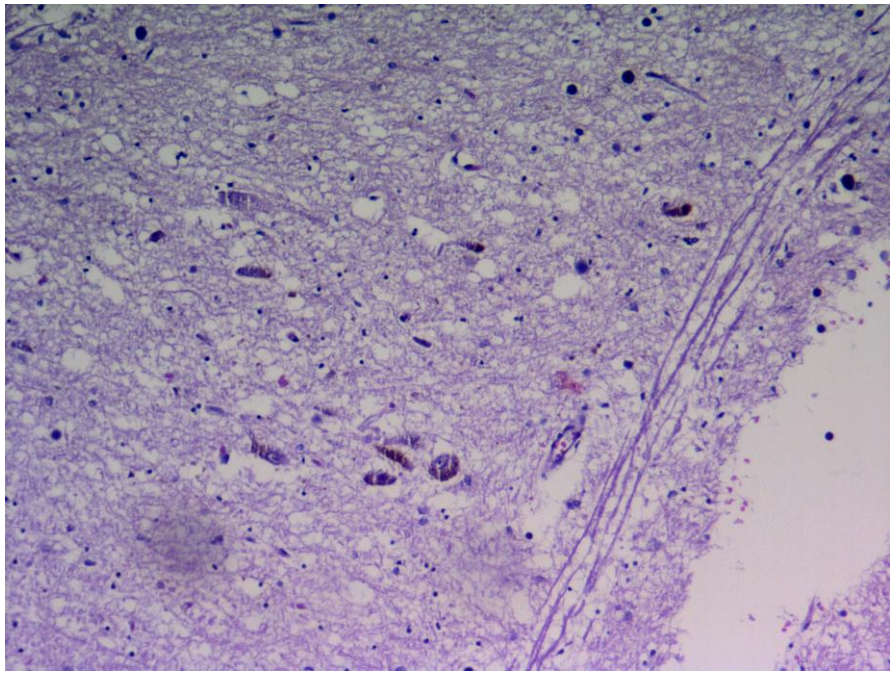
COXI

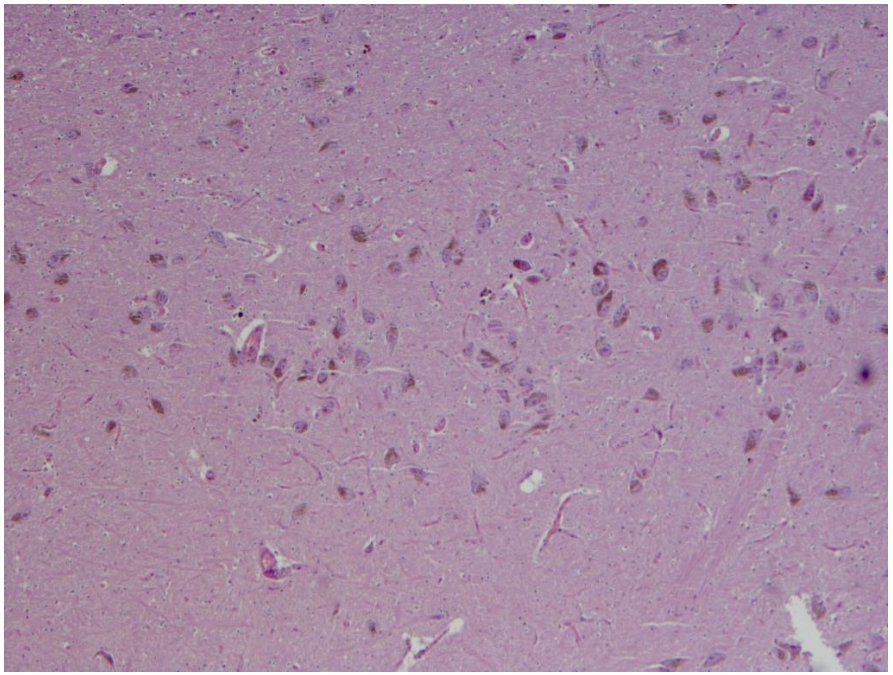


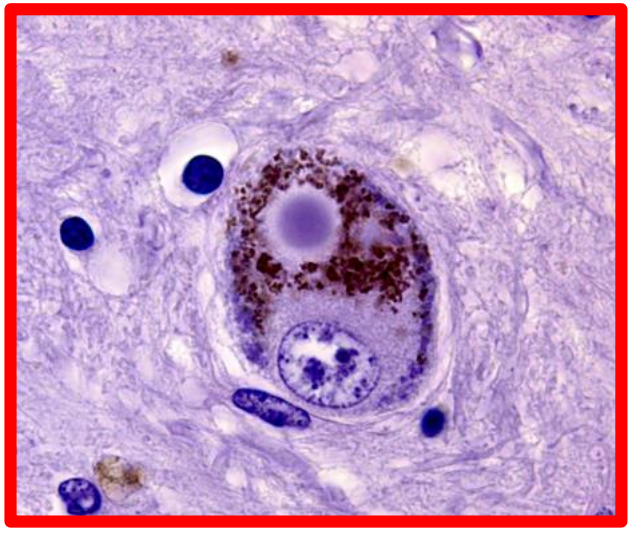
Leukoencephalopathy in MNGIE may be the result of endothelial failure due to thymidine toxicity and mtDNA depletion, which may induce impaired intracerebral blood flow regulation and blood-brain barrier permeability, leading to increased white matter water content.



Extrapyramidal symptoms

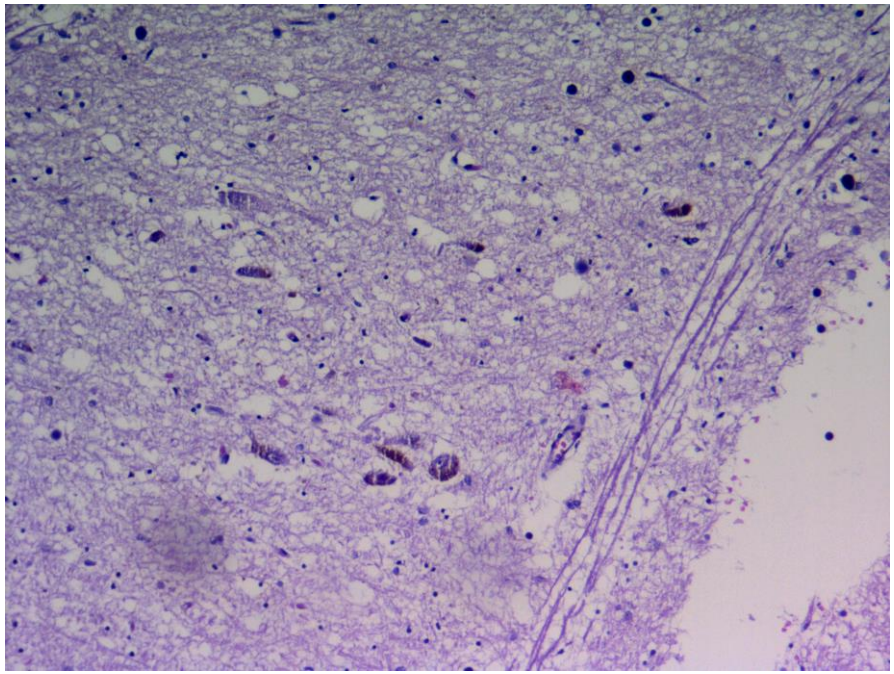


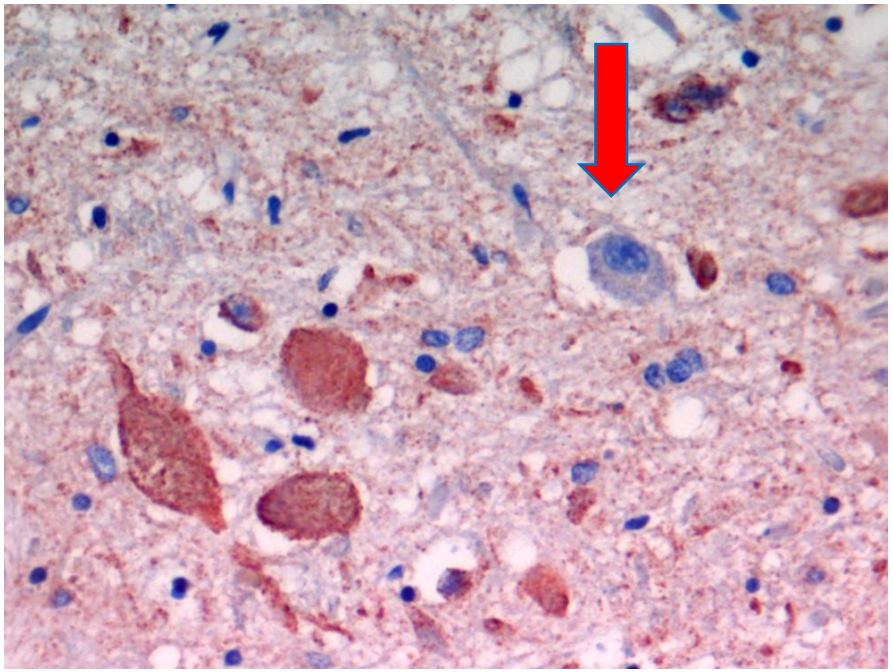


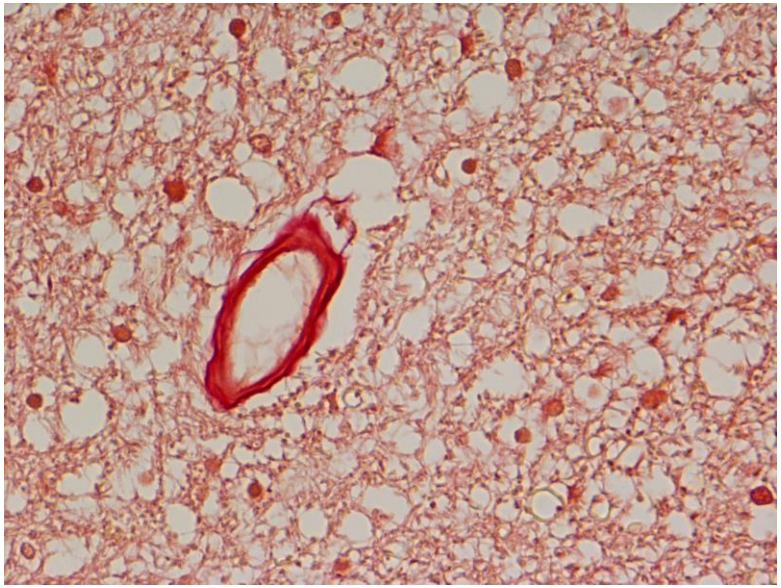


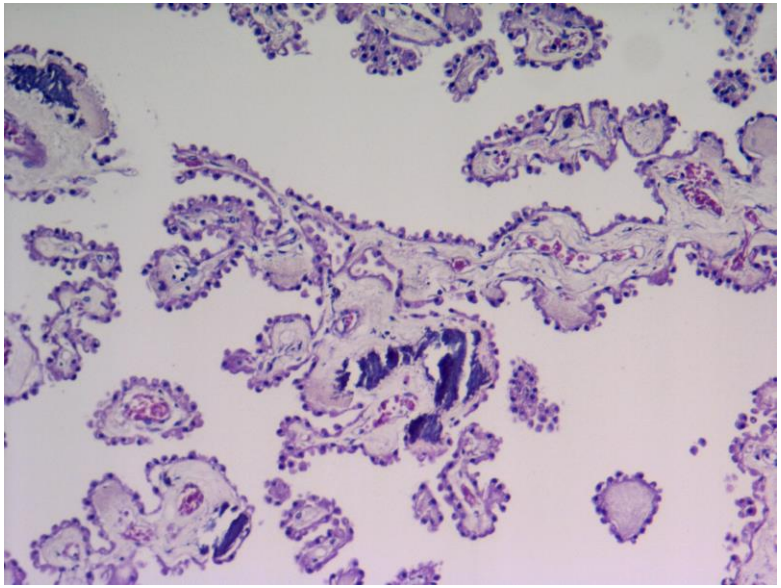
M, CPEO, Parkinson
RNAse H1

Extrapyramidal symptoms



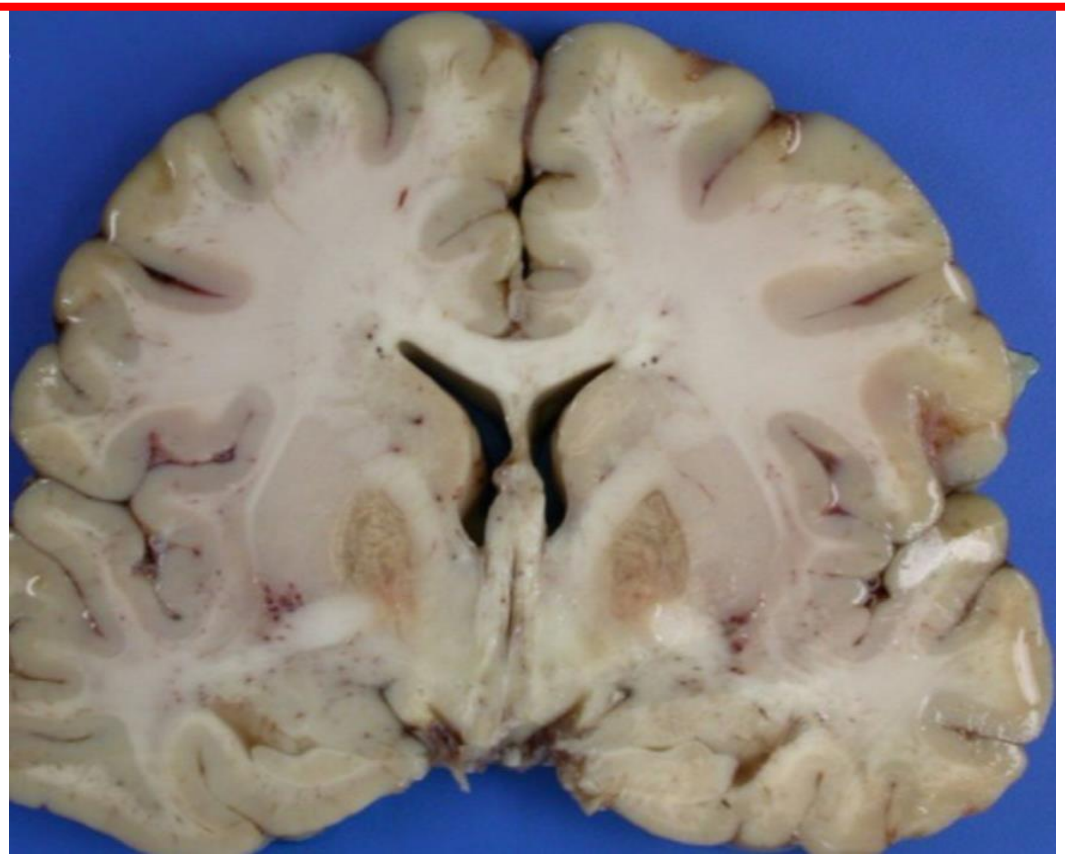






Leigh syndrome

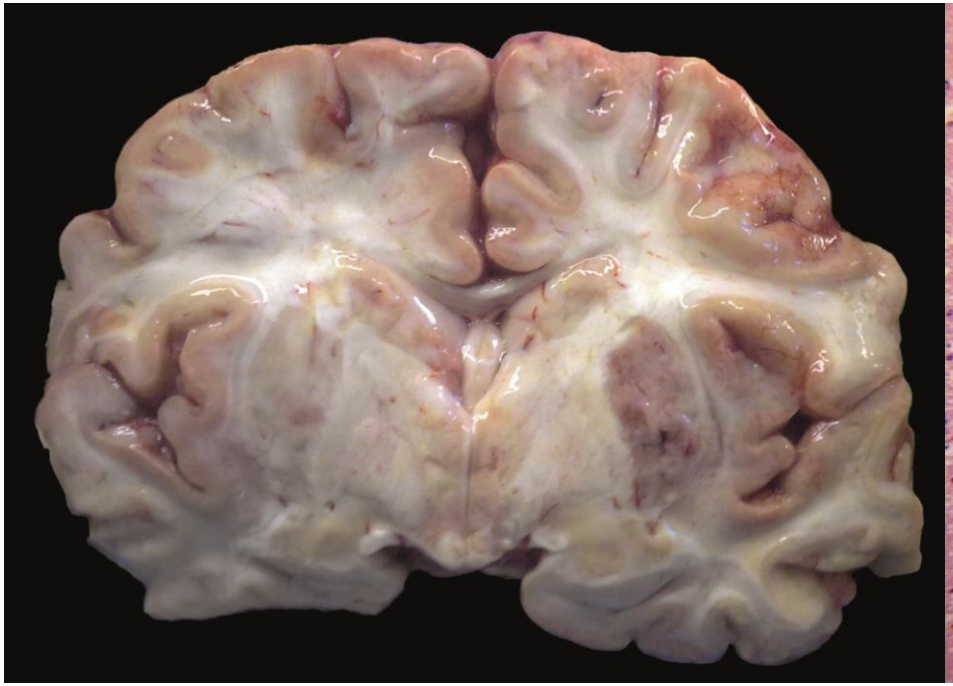
The neuropathological features of Leigh syndrome include symmetrical vasculo-necrotic lesions affecting the substania nigra, putamen in the basal ganglia and thalamus or sub-thalamic nuclei. These lesions are characterized by spongiform changes, and cyto-toxic edema and also increased capillary prominence

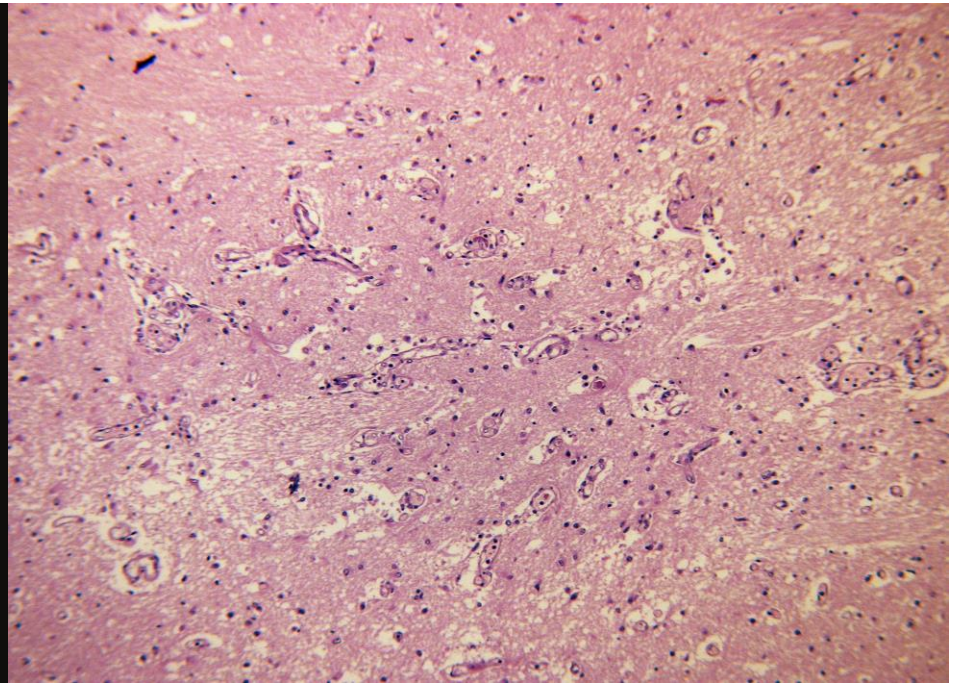


H.E. Turnbull et al. Biochimica et Biophysica Acta 1802 (2010) 111–121

Morphologic evidence of diffuse vascular damage in human and in the experimental model of ethylmalonic encephalopathy

Giordano et al. J Inherit Metab Dis (2012) 35:451–458





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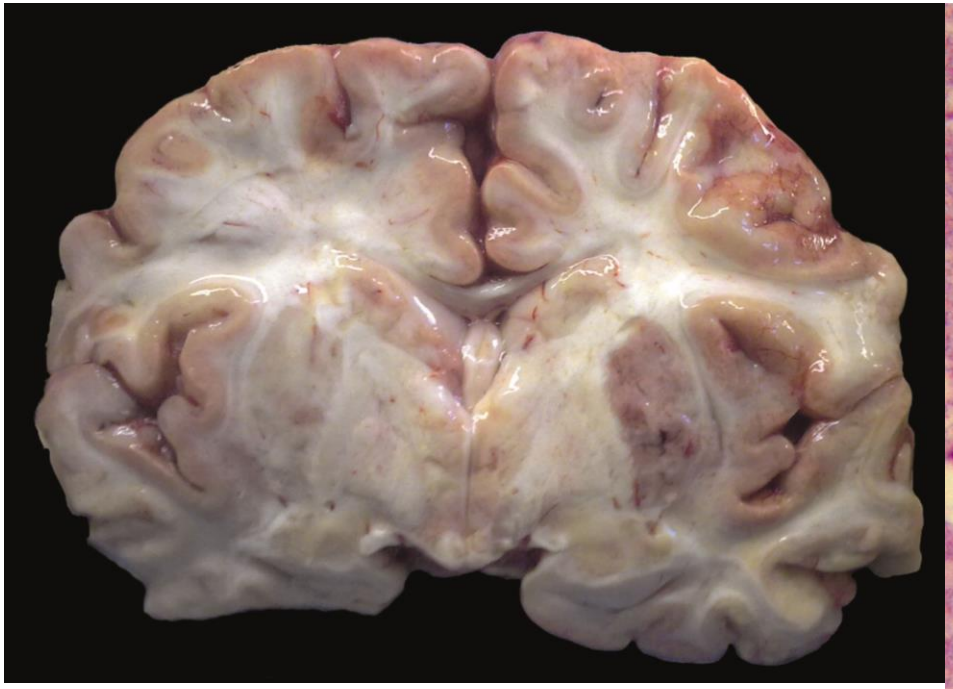

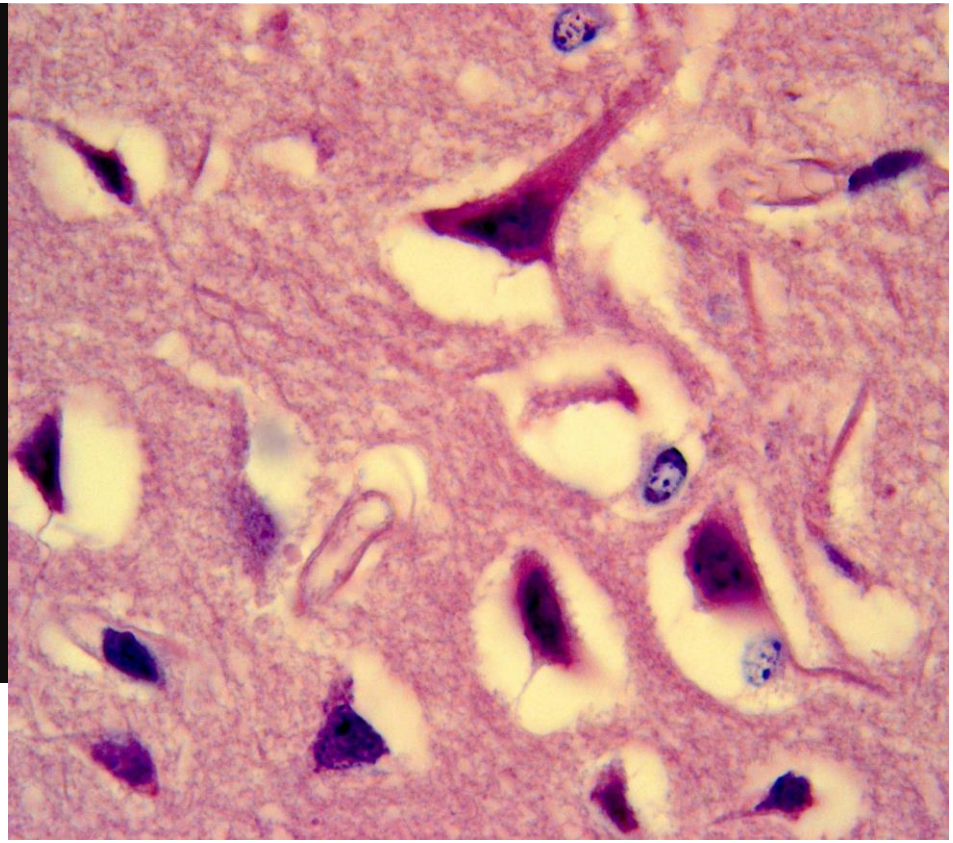

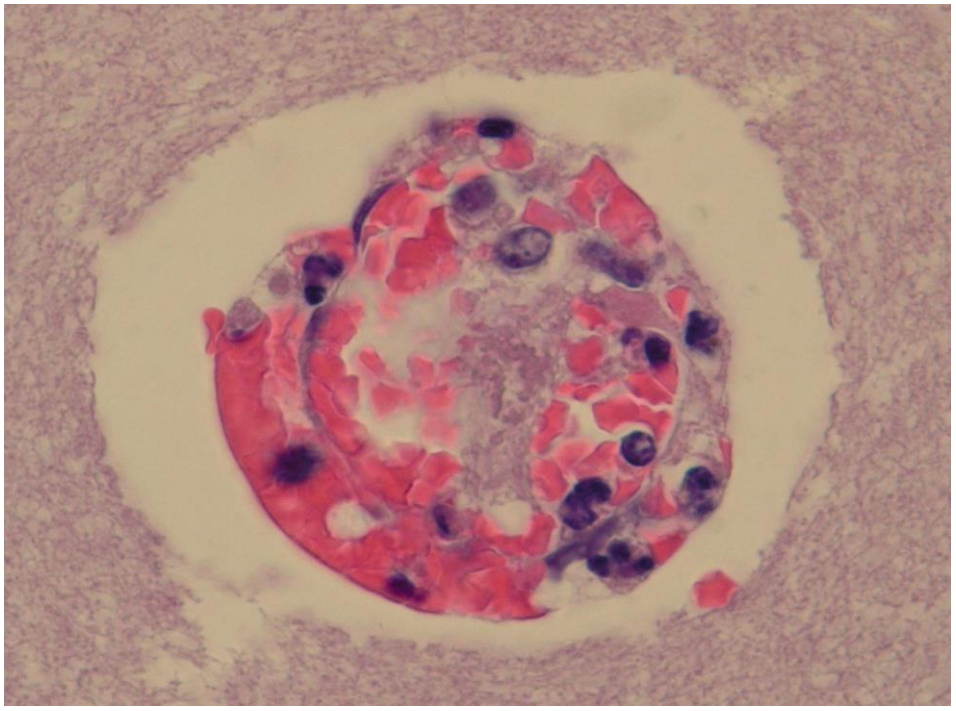

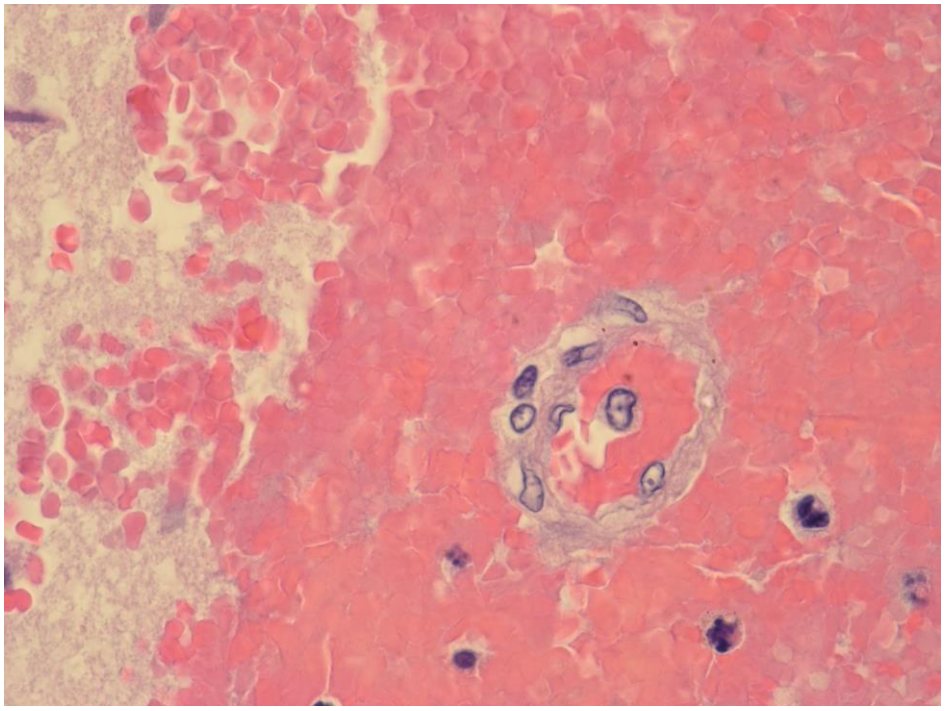

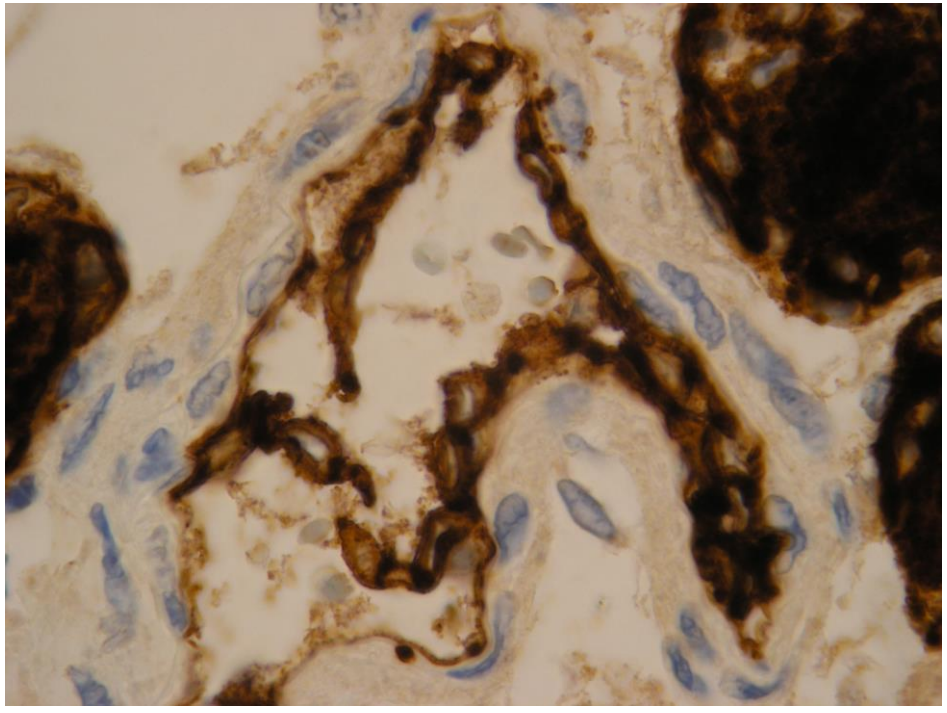

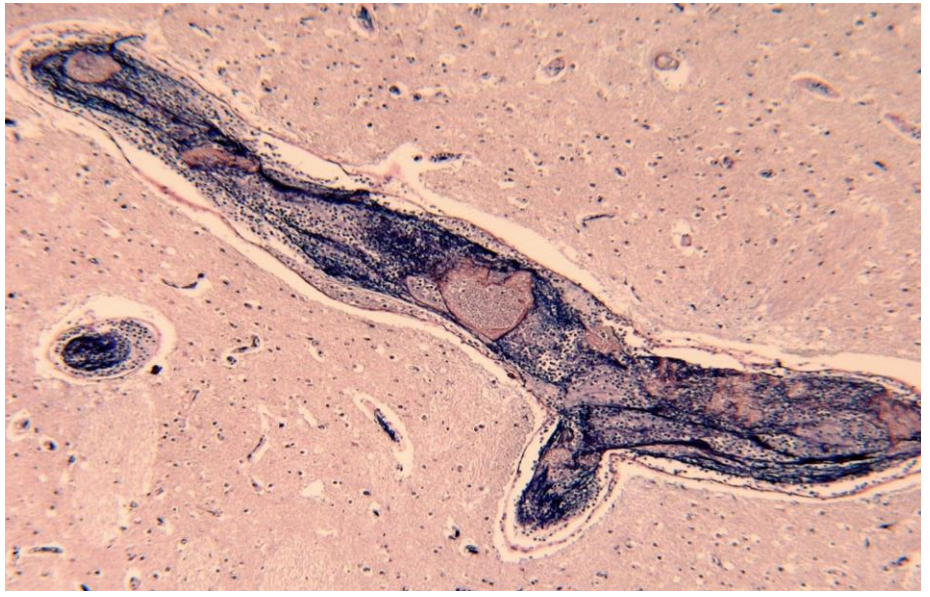

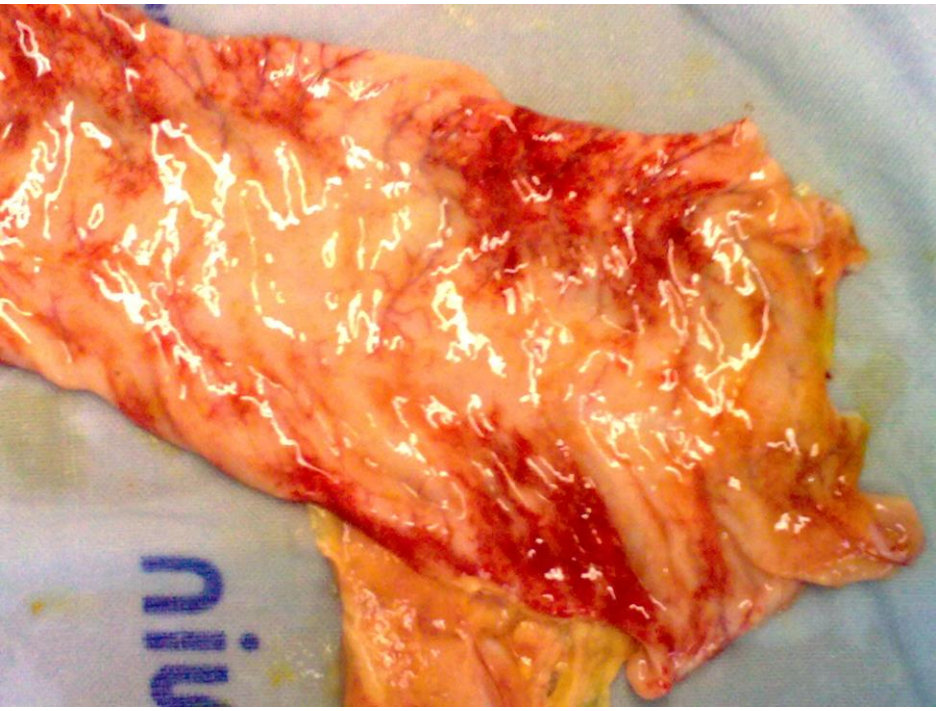

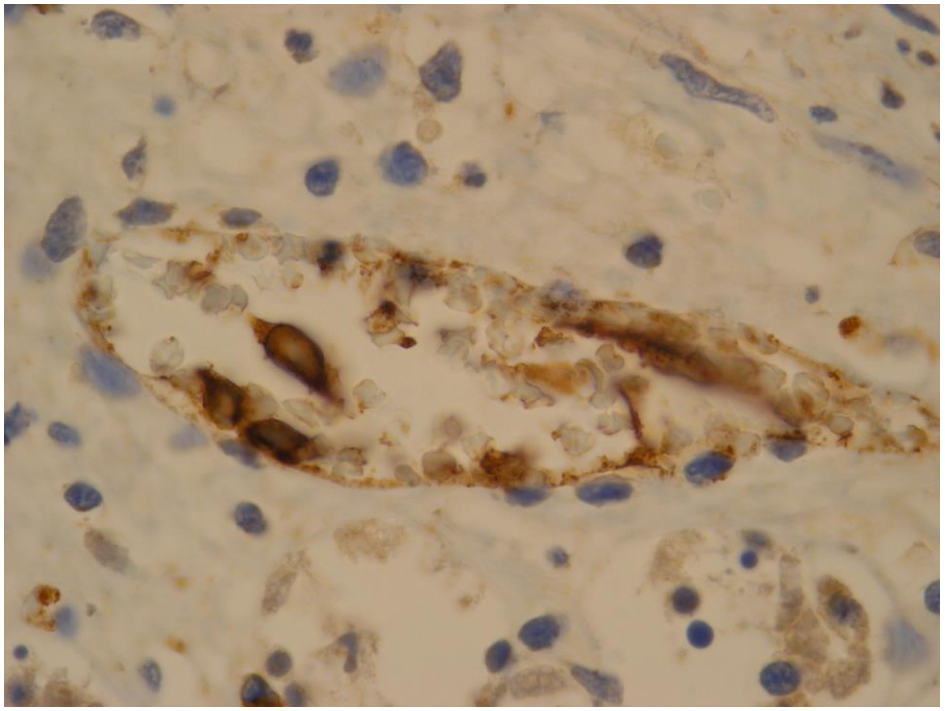

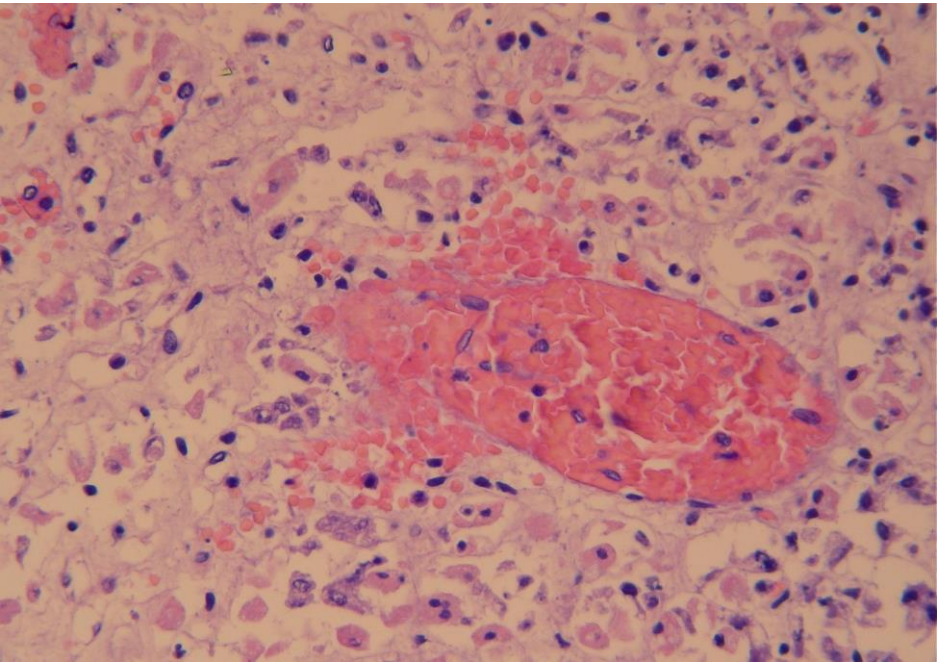

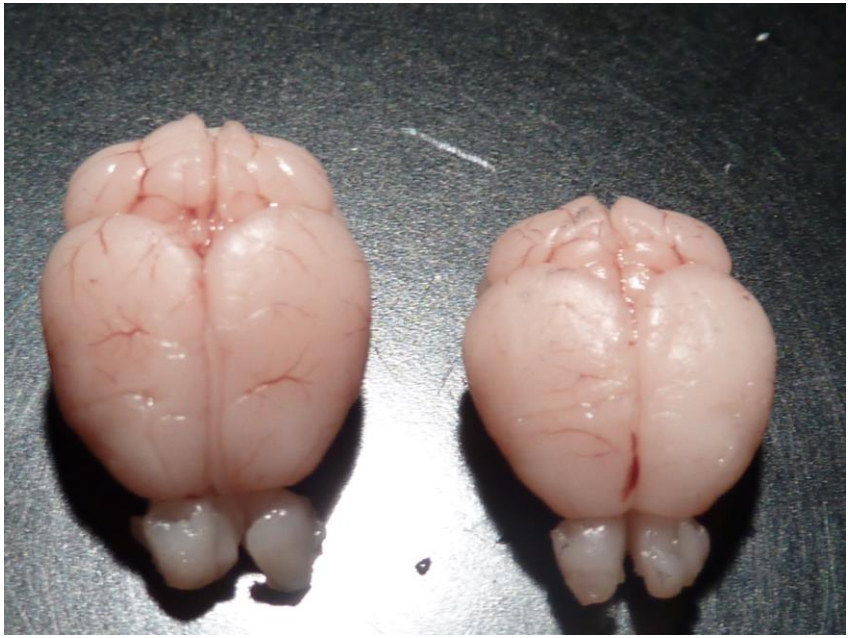

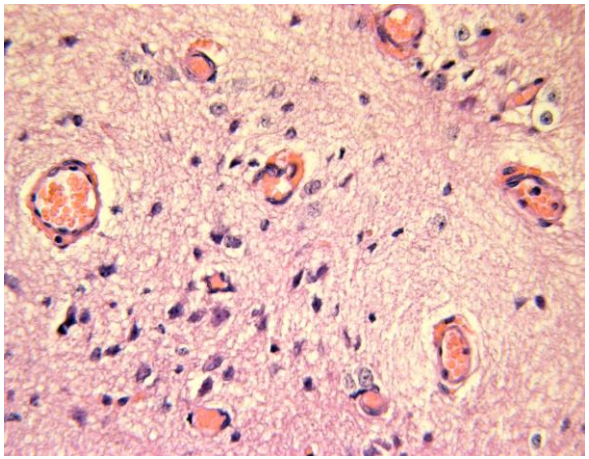

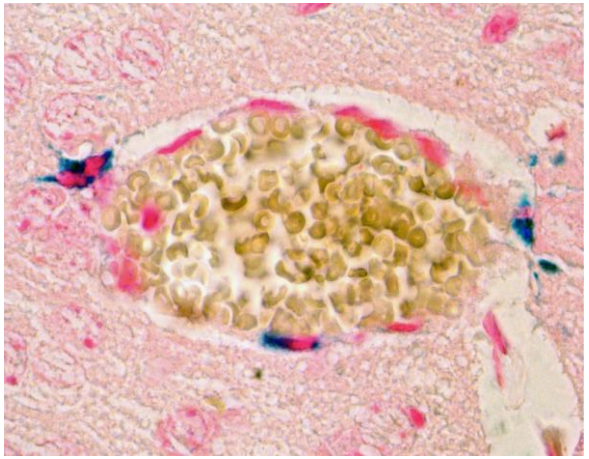

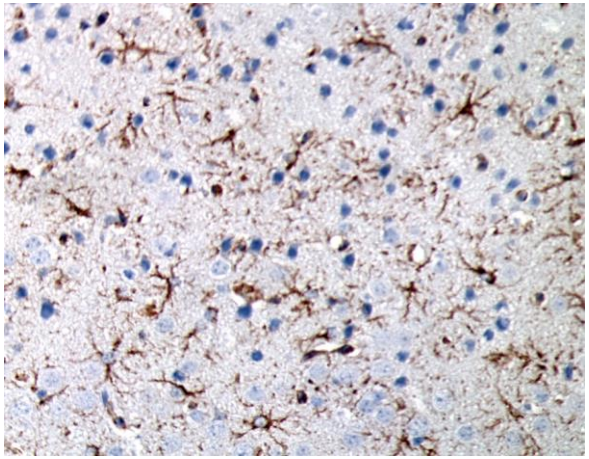


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