

EM of the Adult Brain in the Diagnosis of a Rare Metabolic Disease

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Ghent Pathology 2025

Case: MT

- 38 M, fit & well, married, 2 young daughters, mechanical engineer
- PC: 4-6 weeks of **worsening forgetfulness, personality change, behavioural problems**
- GP arranges admission to local hospital – **April 2024**

- Initial imaging at local hospital: MRI ?lymphoma

- Transferred to tertiary centre for further investigation and management

- **CT-TAP:** No evidence of systemic disease
- **MRI:**
 - Extensive, **symmetrical, bilateral enhancement** involving subcortical **white matter** and white matter tracts
 - Associated vasogenic oedema
 - Sparing of grey matter structures
 - Conclusion: Unusual imaging appearances. Differentials include: diffuse high-grade glioma, neuroinflammatory process, toxic leukoencephalopathy, lymphoma (less likely)

- Neuro-oncology MDT outcome: Admit for brain biopsy

Brain biopsy

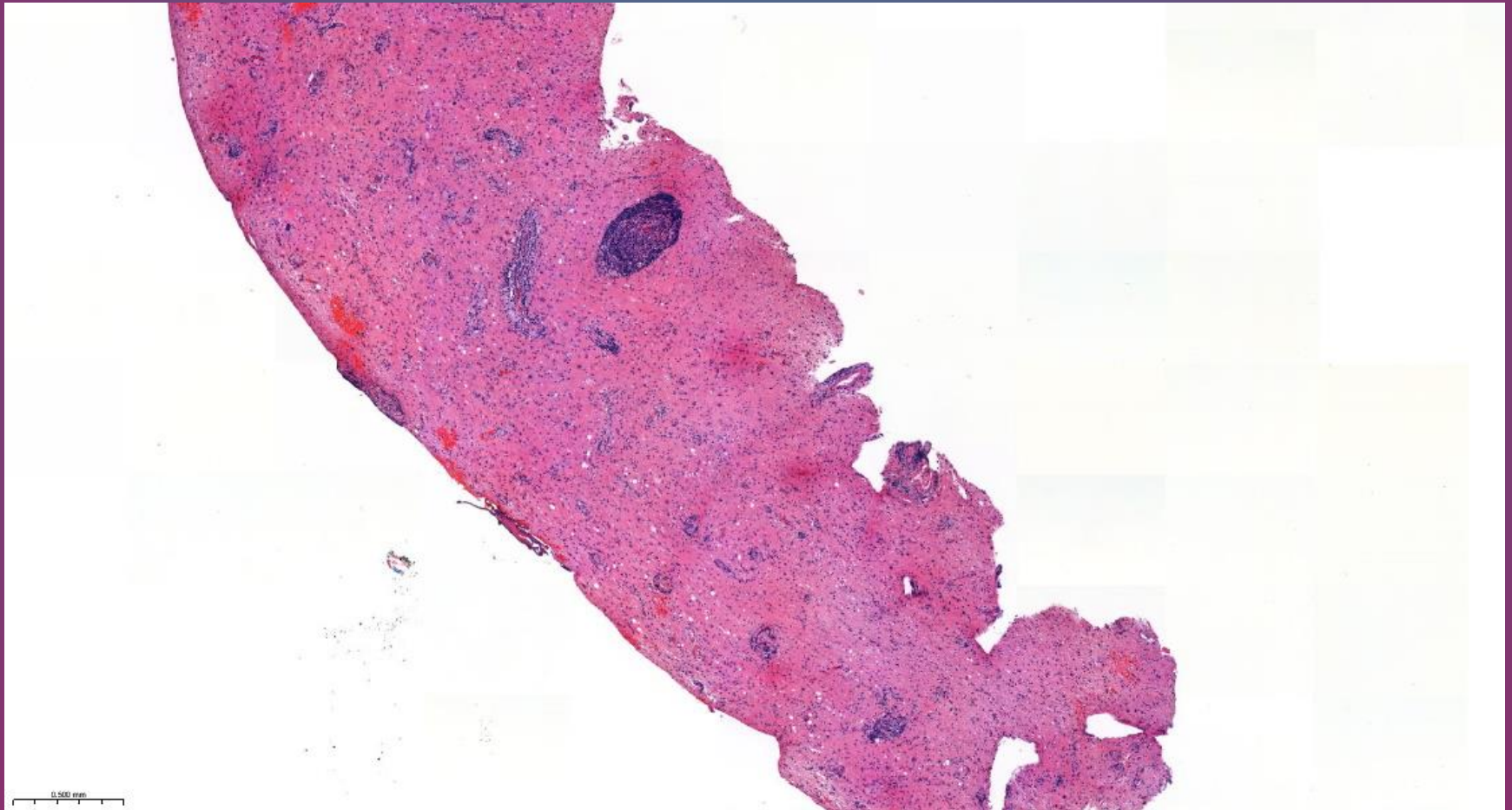
Neuropathology

- Specimen: Right frontal biopsy
- Microscopy:
 - Perivascular infiltrates of small lymphocytes – no atypical lymphocytes/vasculitis
 - Brain parenchyma is hypercellular, scattered astrocytes and foamy macrophages
 - Some cells with large, atypical nuclei and prominent nucleoli
 - IHC & tinctorial stains:
 - **GFAP**: Labels plump astrocytes including those with atypical nuclei
 - **CD68**: Numerous macrophages in parenchyma and perivascularly
 - **CD3**: T-lymphocytes perivascularly and a few infiltrating the parenchyma
 - **CD20/PAX5**: B-lymphocytes perivascularly
 - **SV40**: Negative
 - **LFBCV/NF**: Profound loss of myelin with preservation of axons

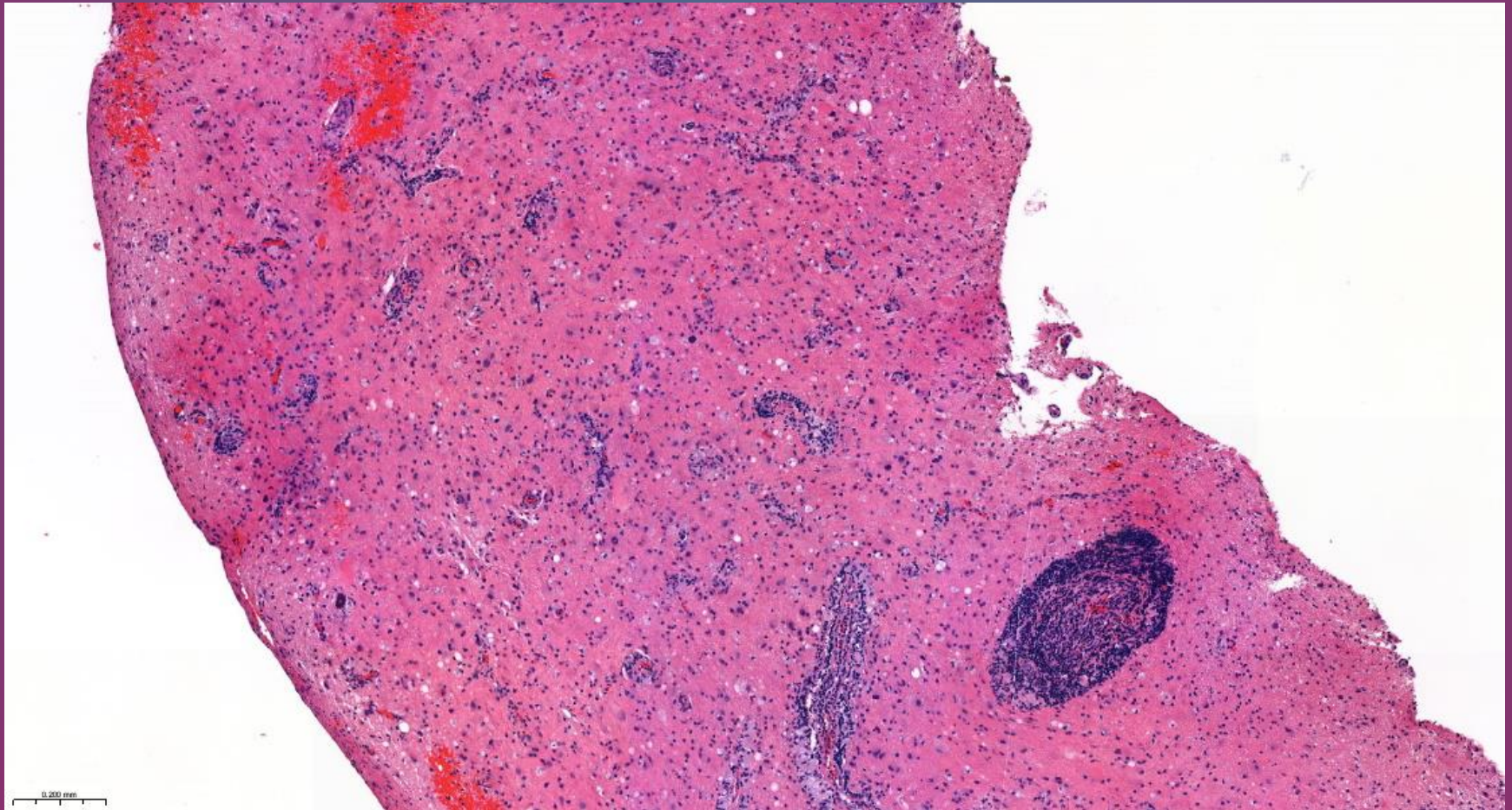
Neuropathology



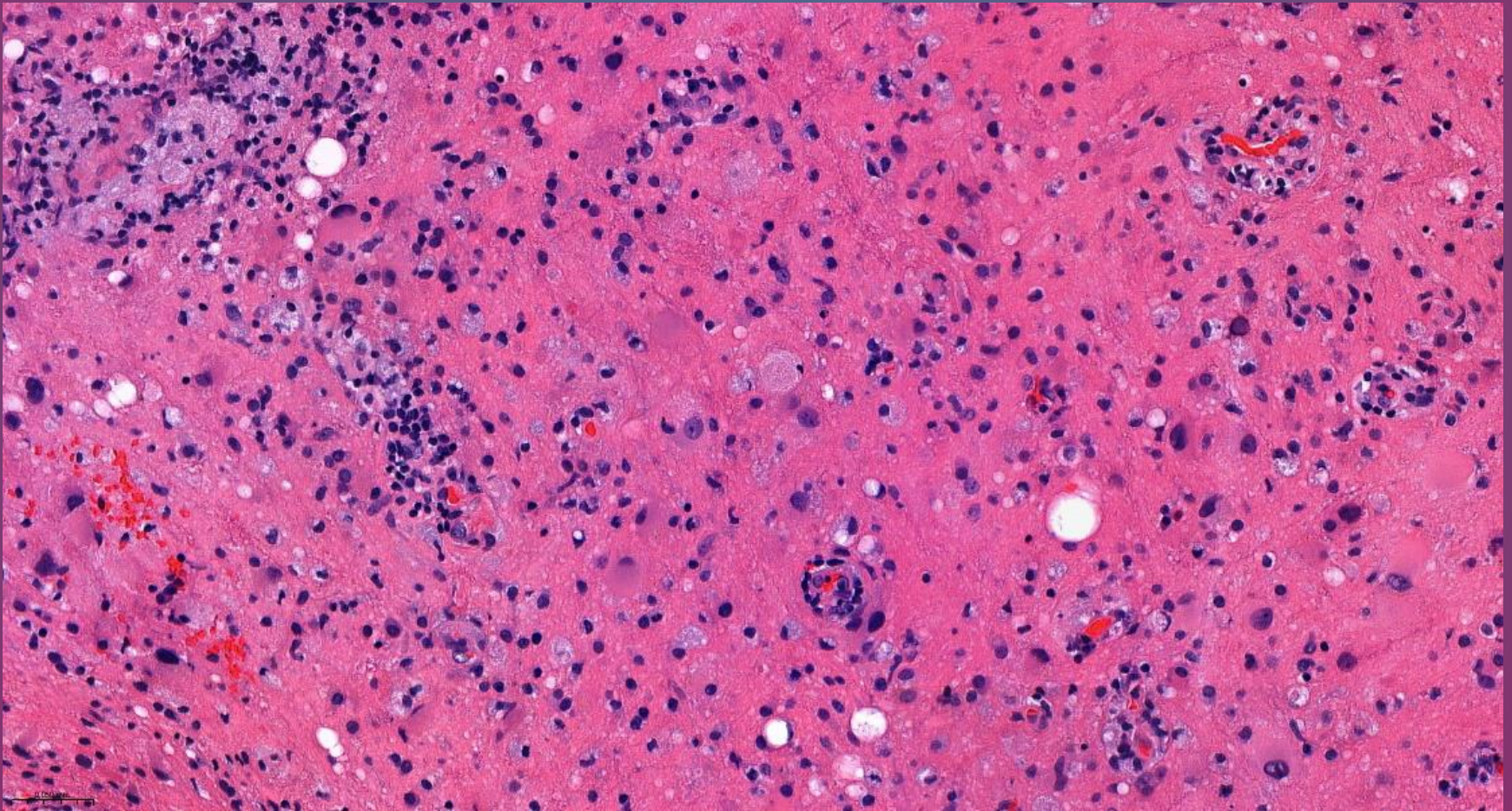
Neuropathology



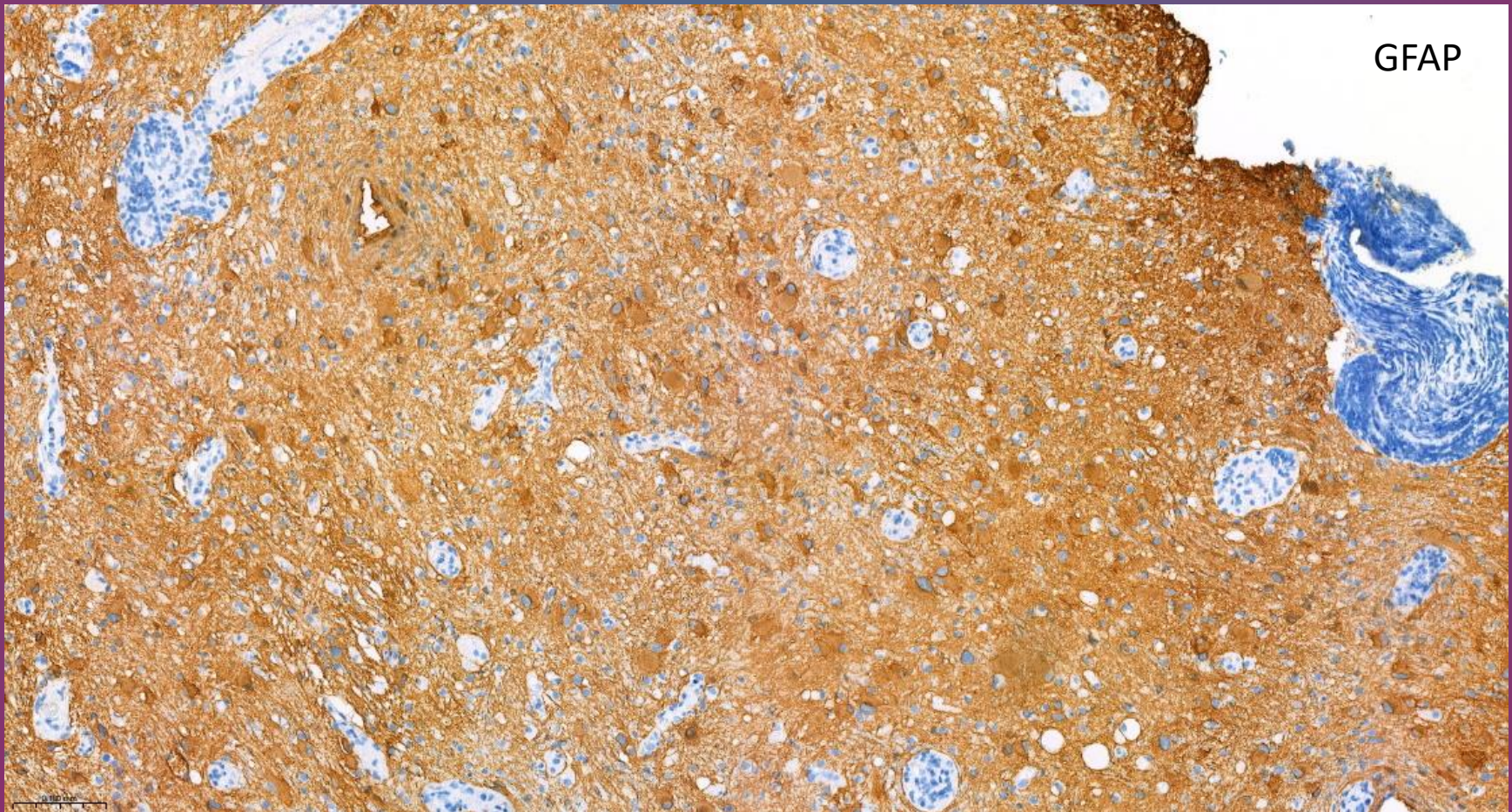
Neuropathology



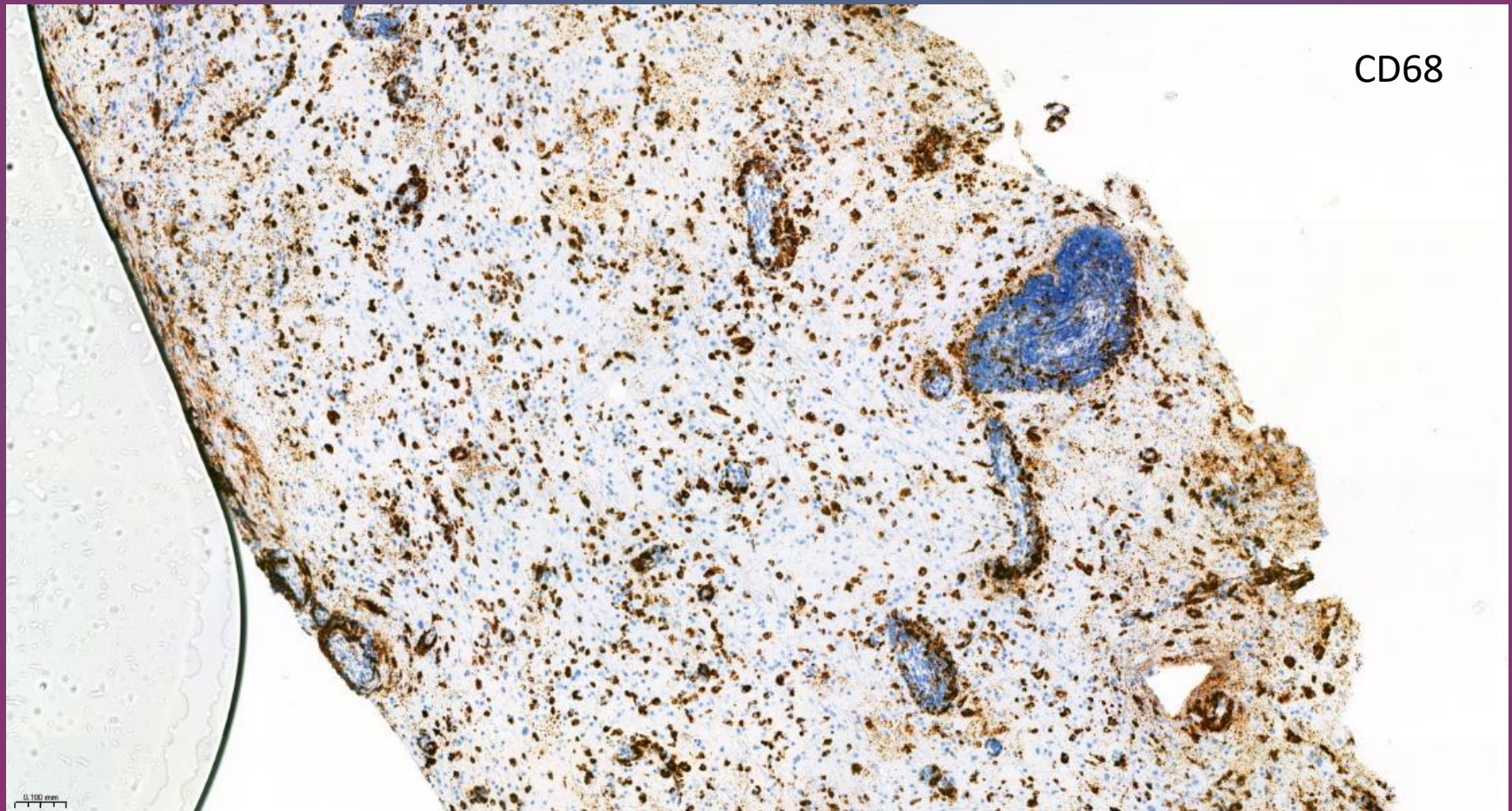
Neuropathology



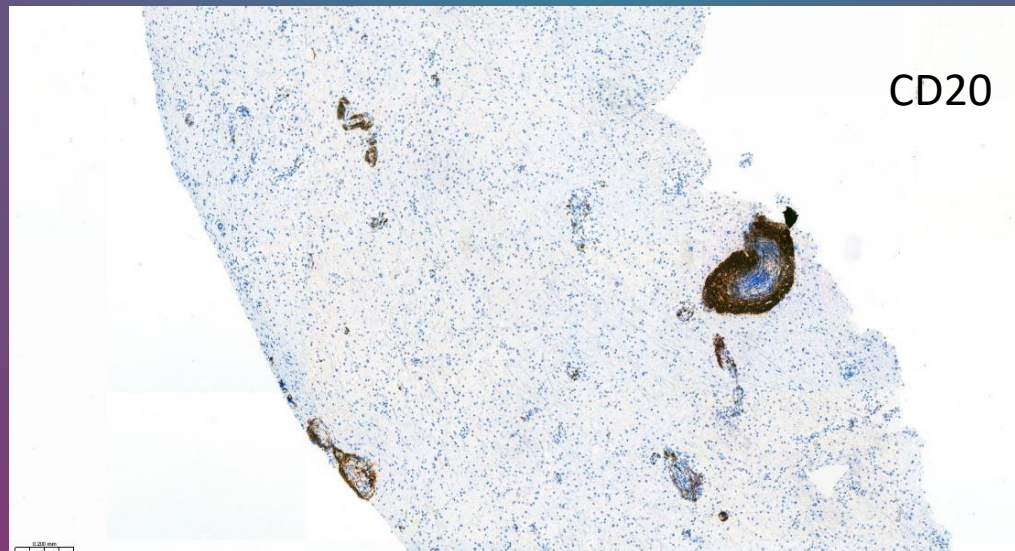
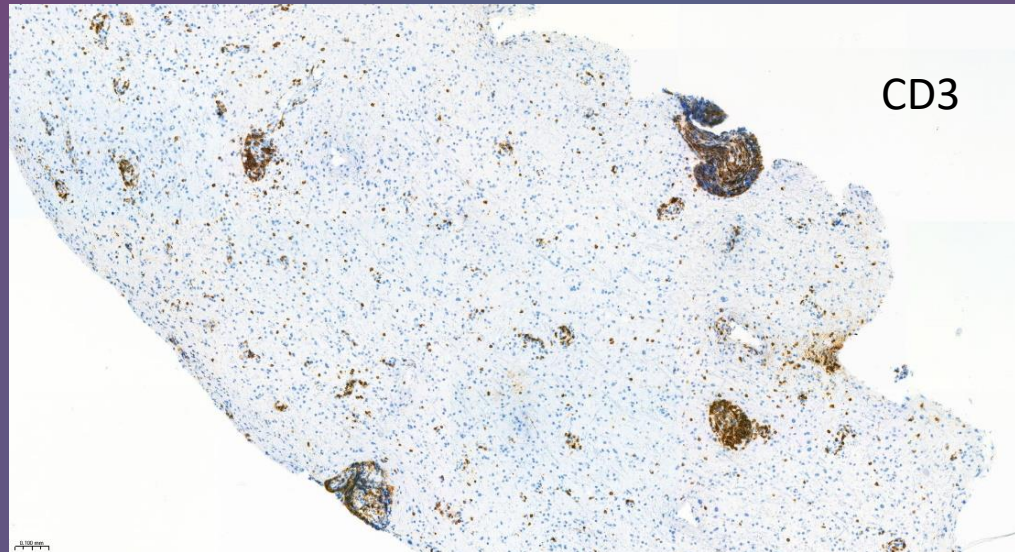
Neuropathology



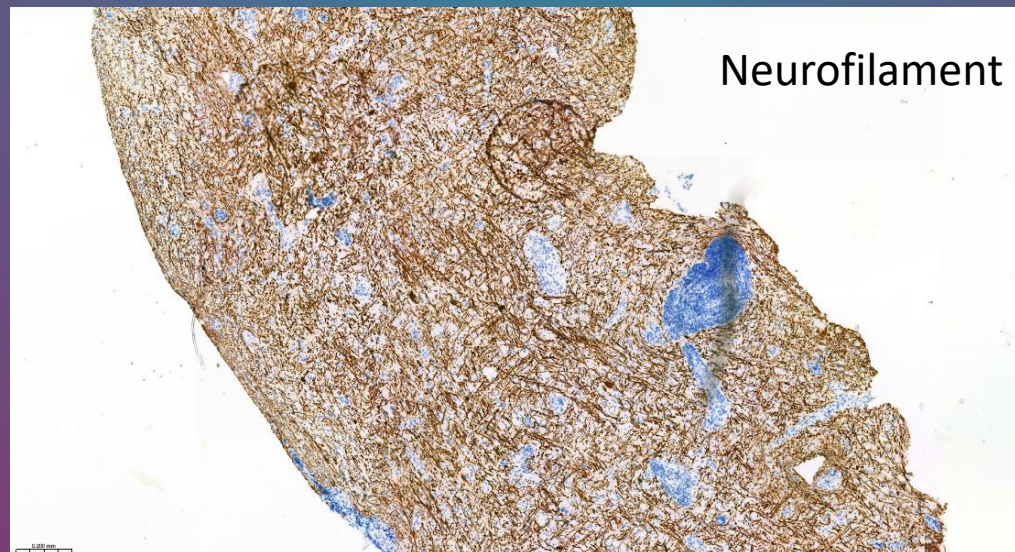
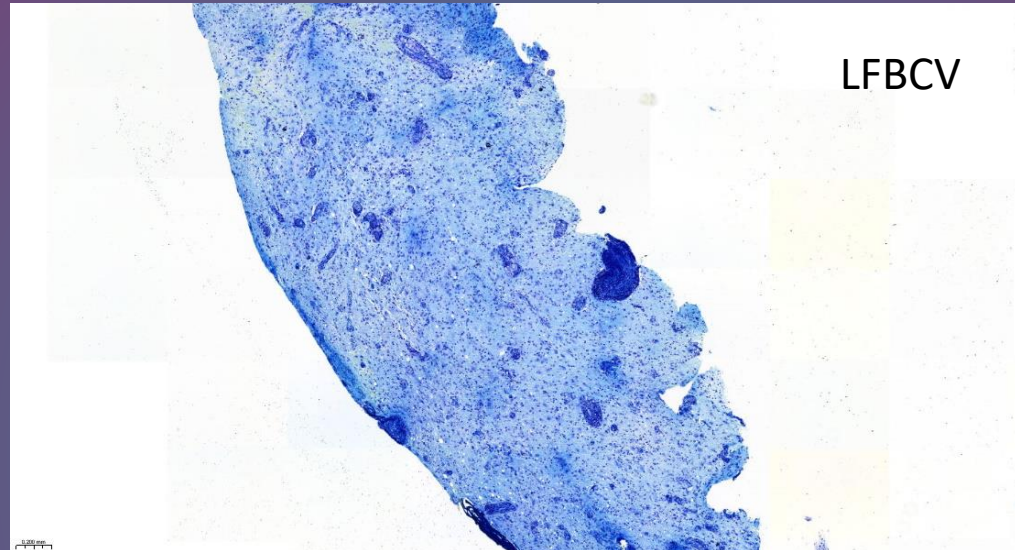
Neuropathology



Neuropathology



Neuropathology



Neuropathology

- Initial conclusions:
 - Loss of myelin with perivascular cuffs of small lymphocytes suggests reactive/inflammatory, probably demyelinating process
 - Atypical nuclei appear to be reactive, no definite neoplastic changes
 - Admixed lymphocytes are small, without atypical nuclei
 - Molecular: Negative for neoplastic variations
 - **REACTIVE/INFLAMMATORY CHANGE WITH DEMYELINATION**

Additional Investigations

- Mitochondrial DNA screening: **Negative**
- Molecular analysis DNA: **Awaited – 3 month turnaround**
- **Biochemistry: Storage disorder screen....**
 - **↑ Very Long Chain Fatty Acids**
 - Neurologists felt this was an atypical presentation and asked for a repeat storage disorder screen
- Referral made to Metabolic Neurology team

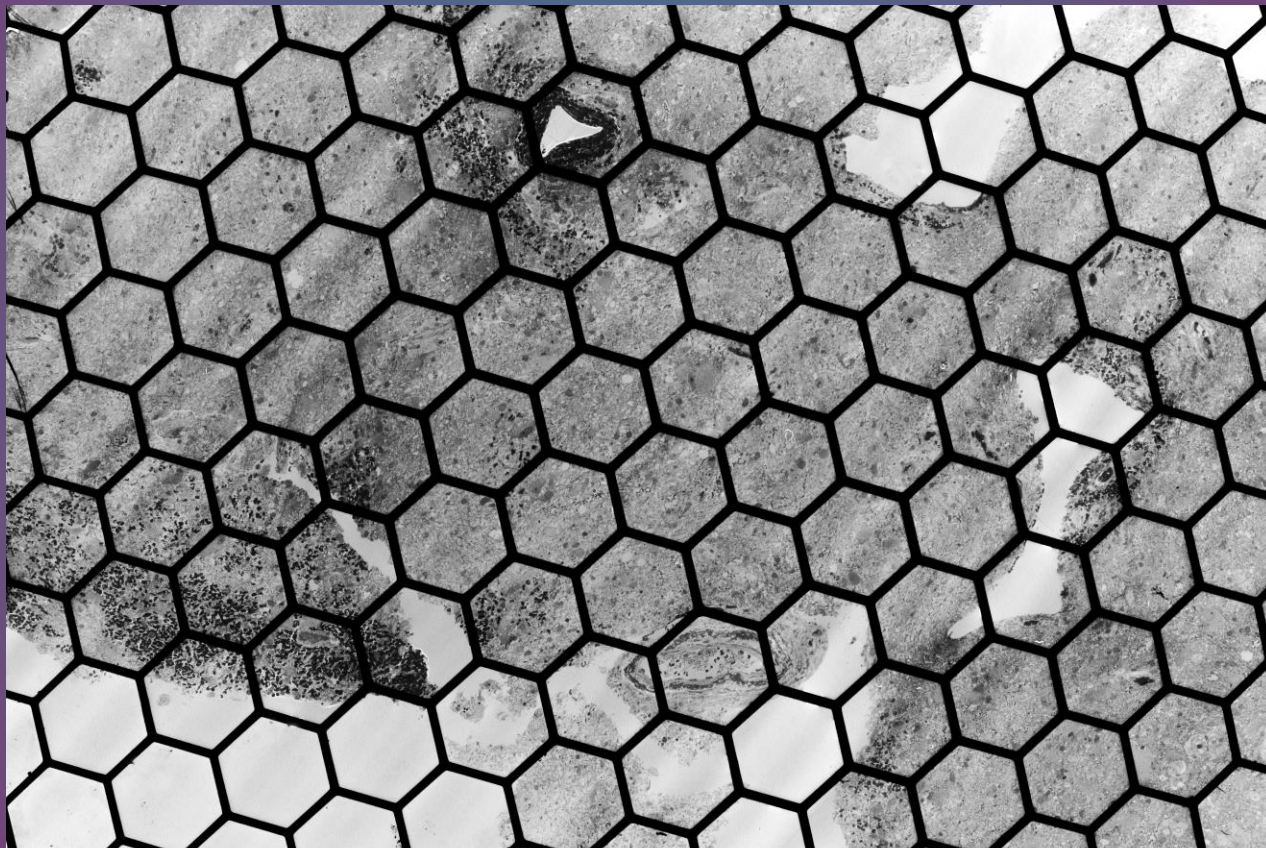
Current clinical status – June 2024

- Over 4 months, clinical deterioration from fit and well →
- Mute
- No engagement
- Doubly incontinent
- Severe dysphagia
- Bedbound, severe limb spasticity
- Admitted under acute neurology services
- **Provisional, suspected diagnosis – pending molecular confirmation**

Back to the brain biopsy....

- **Electron microscopy**
 - Following further info from neurologist
 - Performed from paraffin wax sections
 - Core of tissue dewaxed and processed to resin blocks

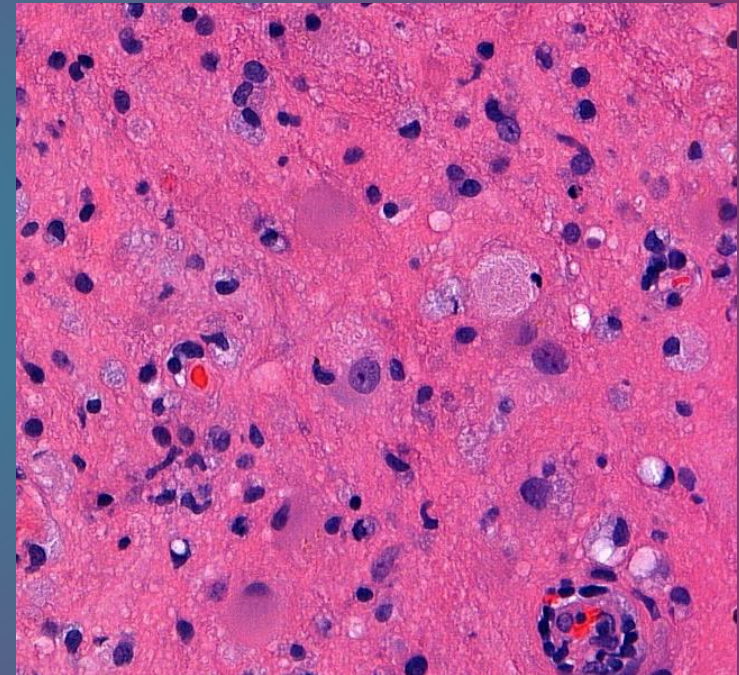
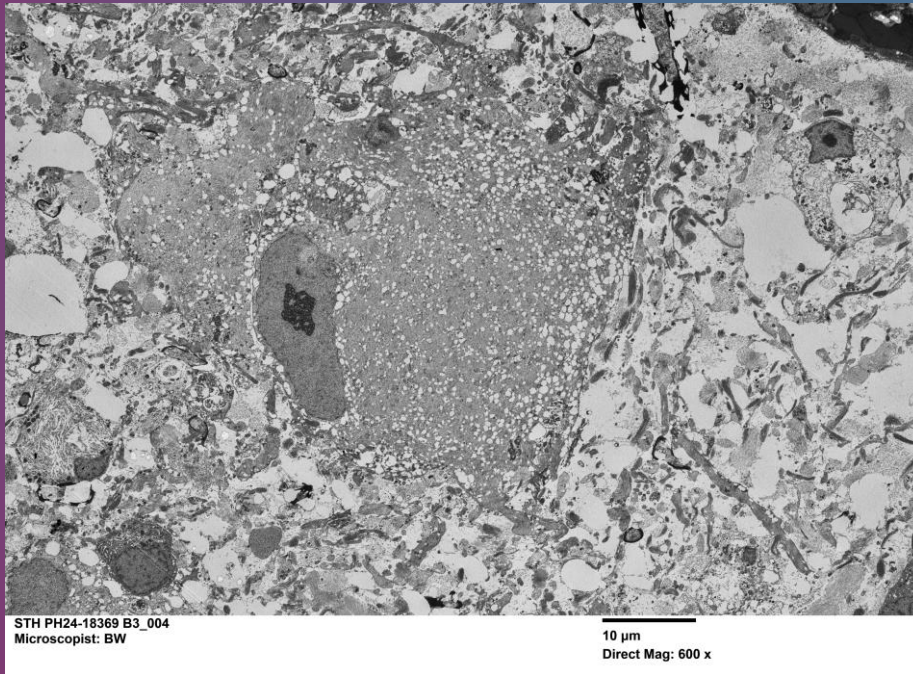
EM of brain biopsy



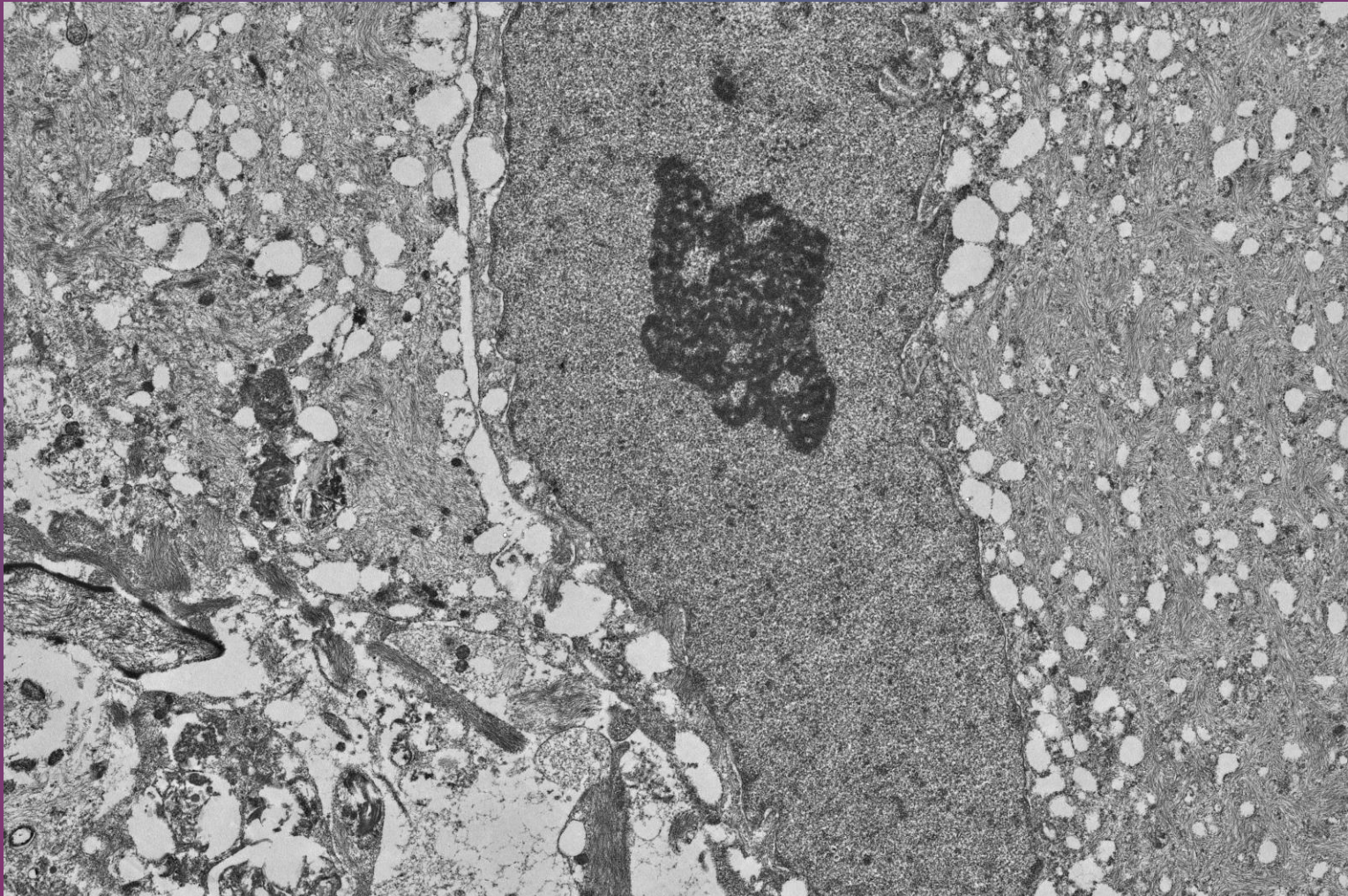
STH PH24-18369 B3_001
Microscopist: BW

10 μ m
Direct Mag: 40 x

EM of brain biopsy



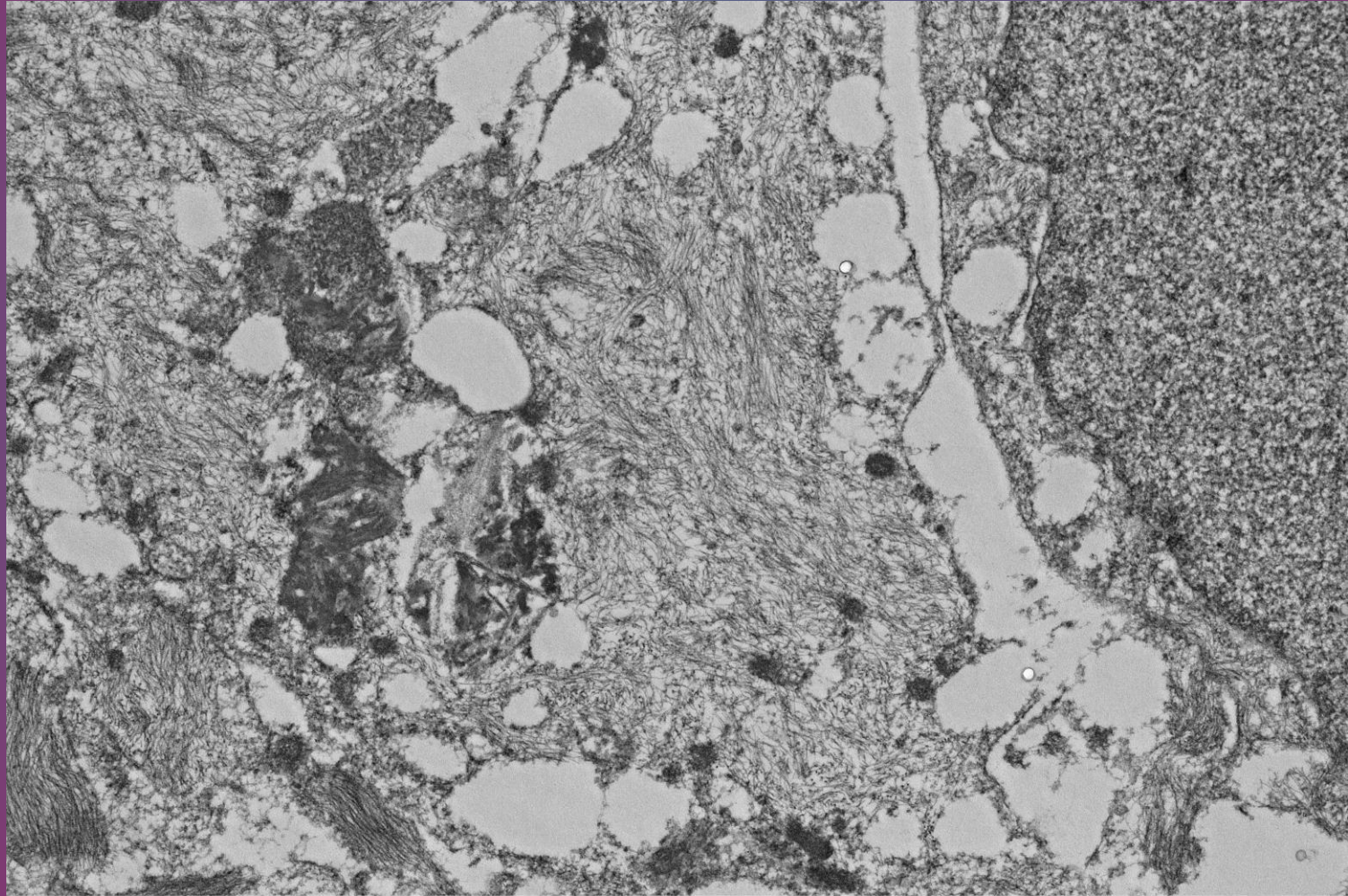
EM of brain biopsy



STH PH24-18369 B3_005
Microscopist: BW

2 μ m
Direct Mag: 2500 x

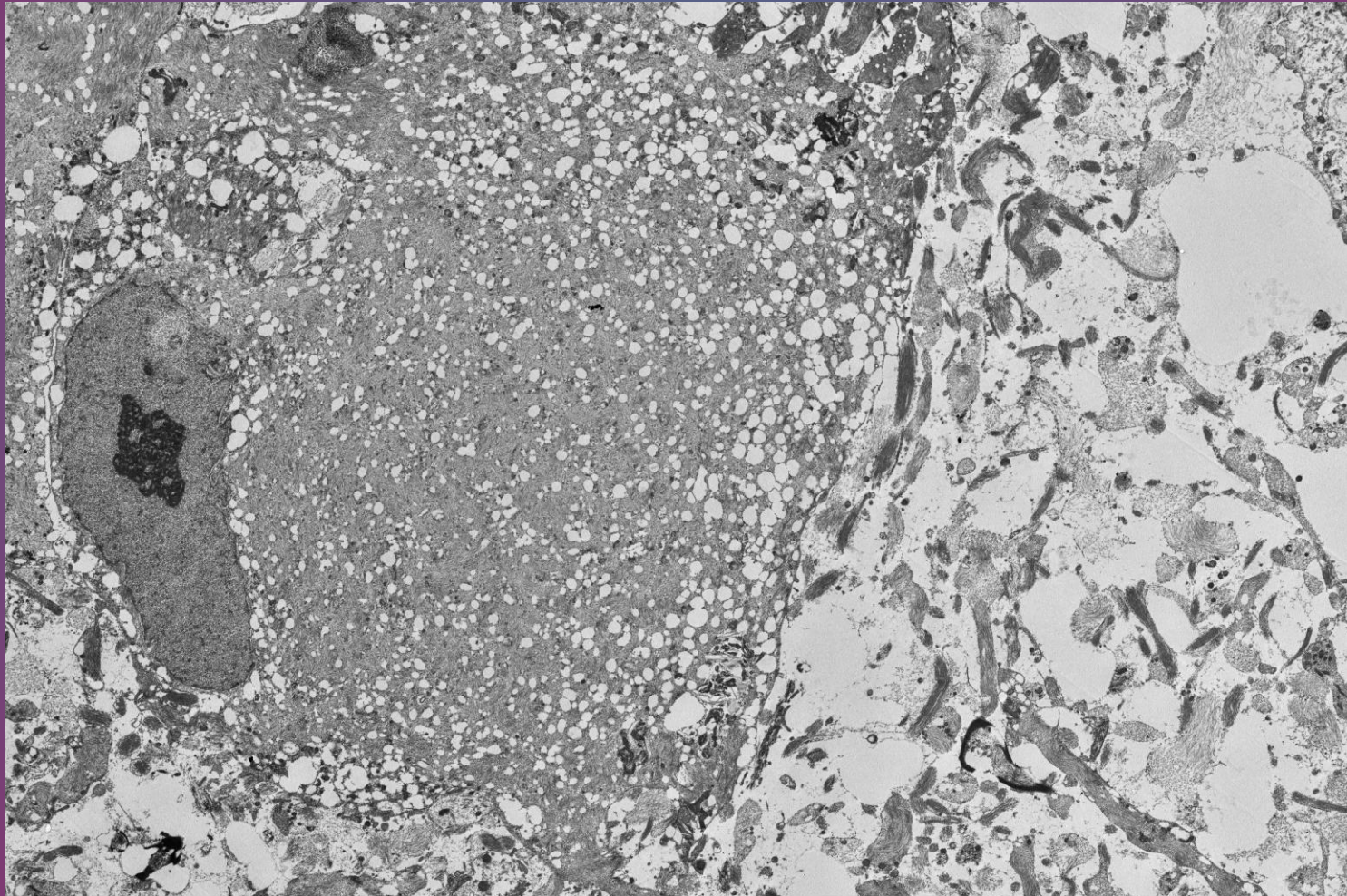
EM of brain biopsy



STH PH24-18369 B3_006
Microscopist: BW

800 nm
Direct Mag: 8000 x

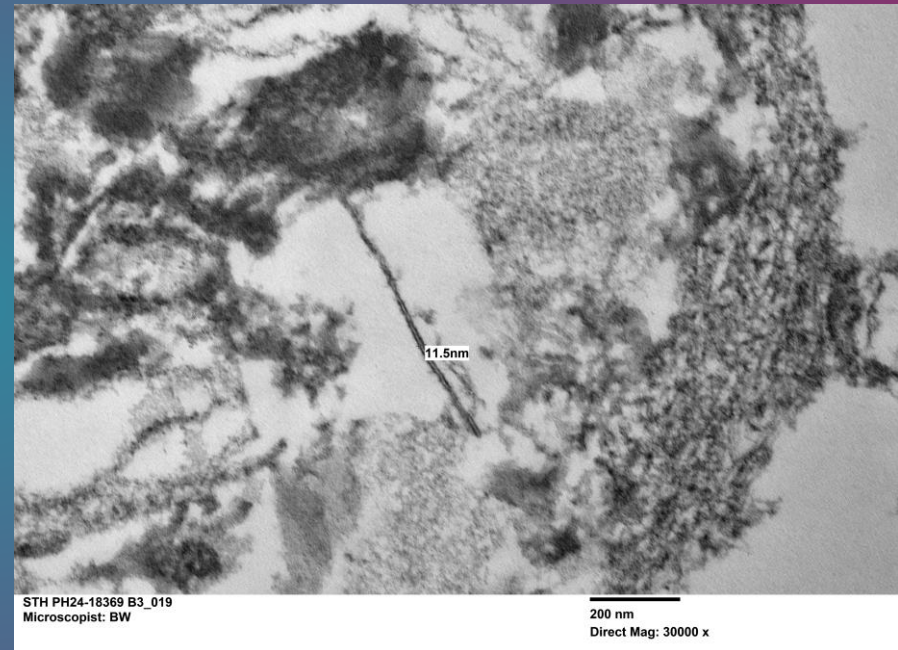
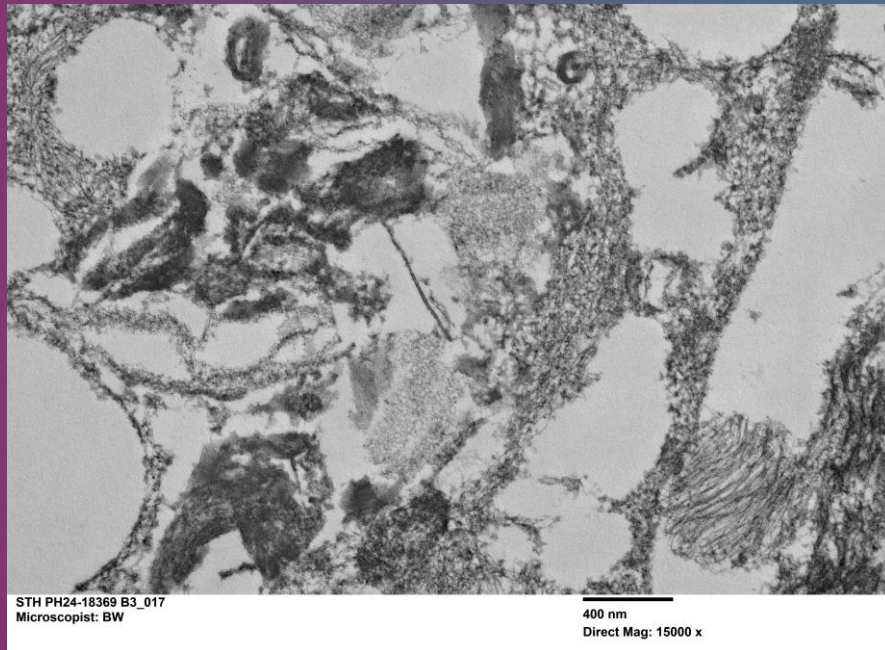
EM of brain biopsy



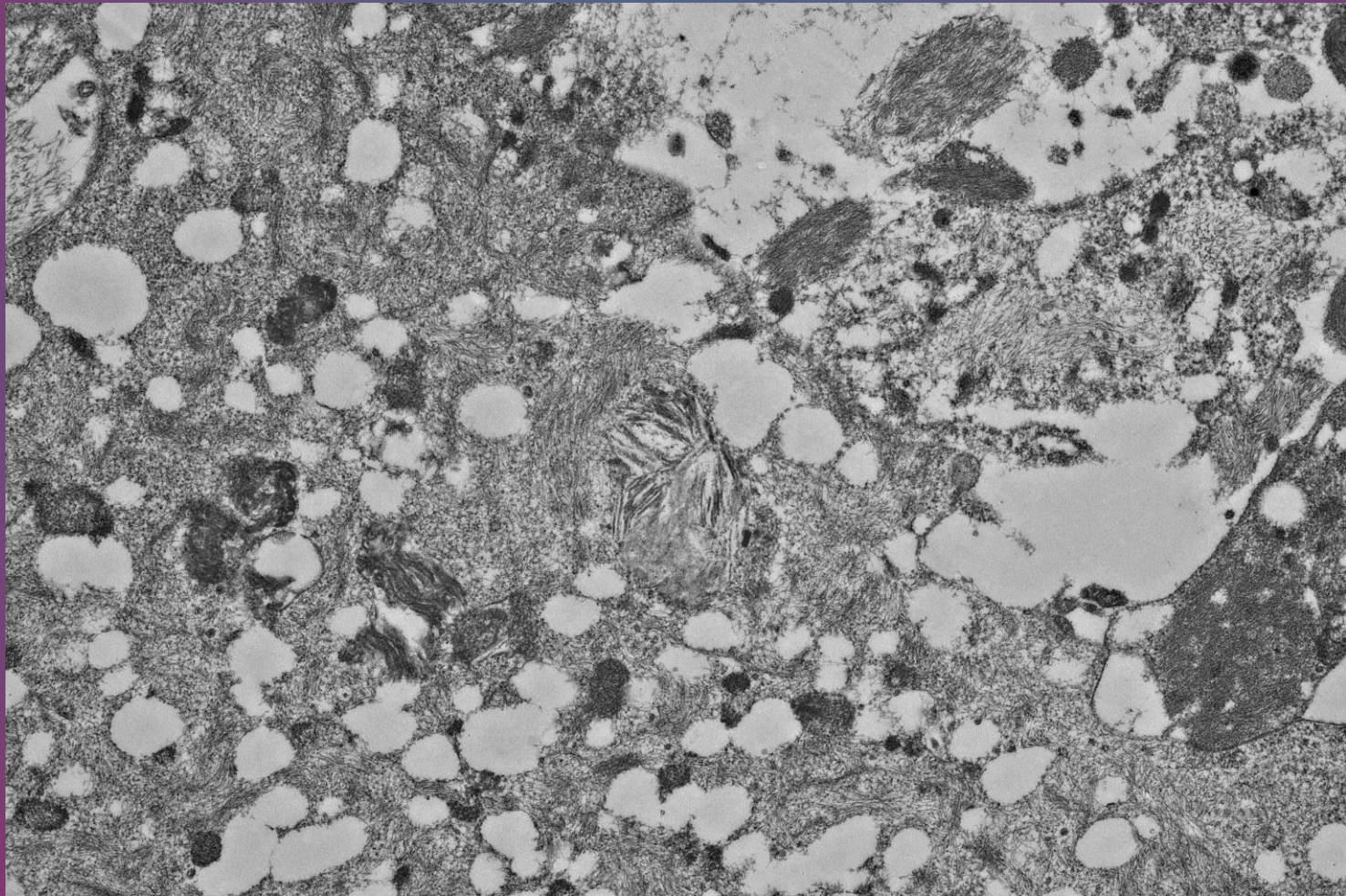
STH PH24-18369 B3_015
Microscopist: BW

6 μ m
Direct Mag: 1000 x

EM of brain biopsy



EM of brain biopsy



STH PH24-18369 B3_021
Microscopist: BW

1 μ m
Direct Mag: 5000 x

EM of brain biopsy



STH PH24-18369 B3_022
Microscopist: BW

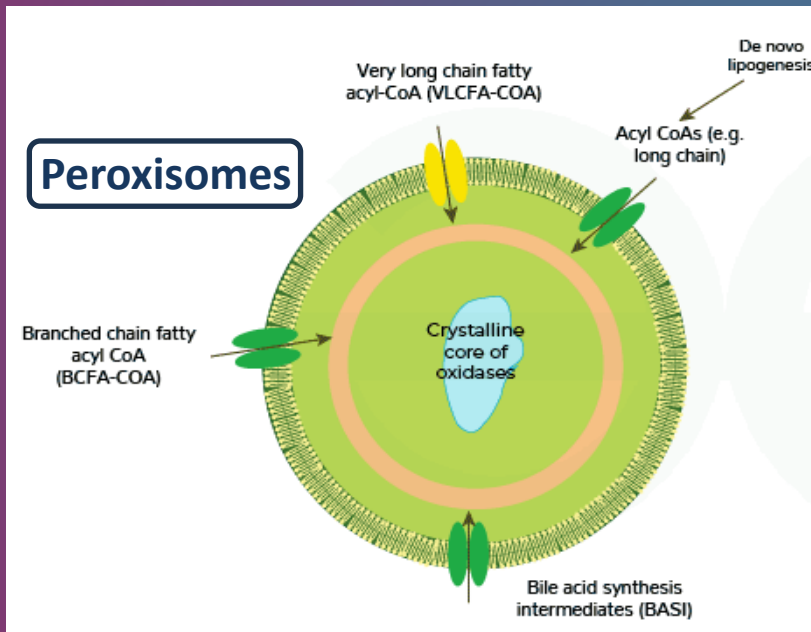
200 nm
Direct Mag: 25000 x

Provisional diagnosis

- Clinically:
 - Severe cognitive impairment
 - Limb spasticity
 - Bladder dysfunction
 - Bulbar dysfunction
- Biochemistry:
 - Elevated Very Long Chain Fatty Acids
- Histology:
 - Reactive change and demyelination
- Electron Microscopy:
 - Reactive astrocytes containing lysosomes with trilamellar crystalline inclusion bodies

X-linked adrenoleukodystrophy

Peroxisomal Disorders

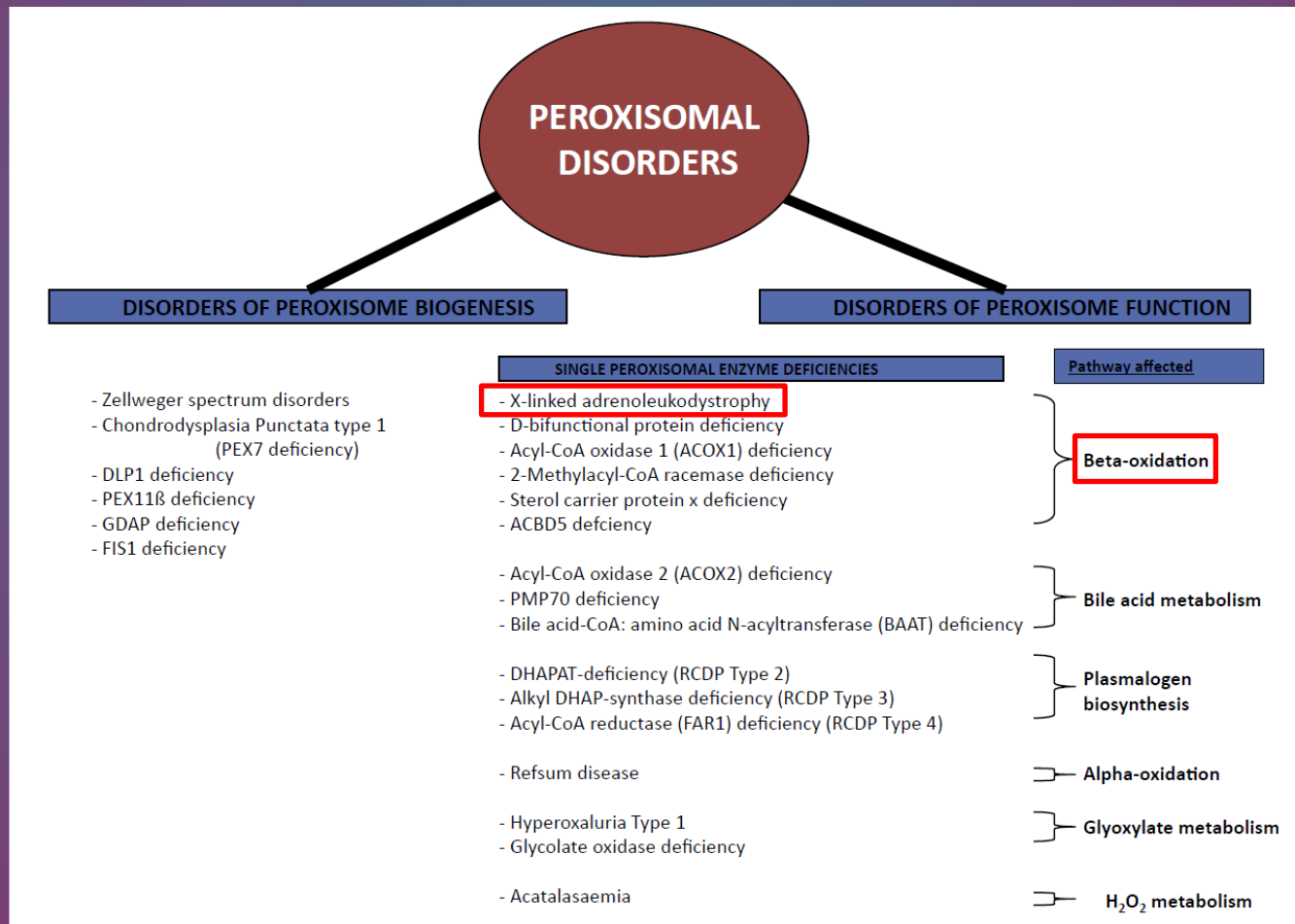


<https://www.geeksforgeeks.org/peroxisomes-functions-diagram/>

Functions of Peroxisomes

- Fatty acid oxidation
- Hydrogen peroxide metabolism
- Lipid biosynthesis
- Plasmalogen synthesis
- Oxidation of phytanic acid
- Catabolism of purines, polyamines and amino acids

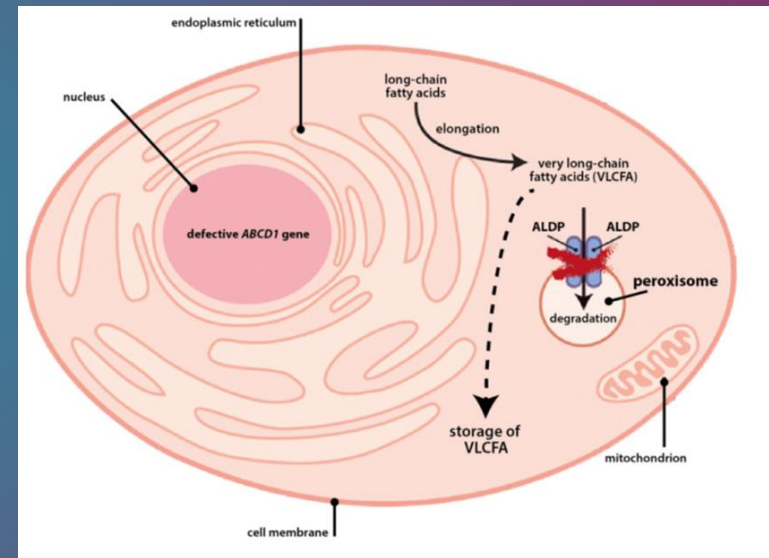
Peroxisomal Disorders



Wanders RJA. Peroxisomal disorders: Improved laboratory diagnosis, new defects and the complicated route to treatment. Mol Cell Probes. 40; (2018) 60-69

X-linked adrenoleukodystrophy

- Rare, genetic disorder:
 - Degradation of the white matter
 - Degradation of the adrenal cortex
- *ABCD1* gene, located on the X-chromosome
- Impaired VLCFA transport into the peroxisome
- ↑ VLCFAs = Degradation of white matter tracts and adrenal cortex



Vlachou S., Kanakis G., Kaltsas G. Adrenal insufficiency due to X-linked adrenoleukodystrophy. In: Feingold KR, Ahmed SF, Anawalt B, et al., editors. Endotext [Internet]. South Dartmouth (MA): MDTText.com, Inc.; 2000.

Management of x-ALD

- **Possibility of effective treatment if detected at very early stage**
 - Stem cell transplantation (SCT)
 - Steroid replacement therapy
 - Physiotherapy
 - Occupational therapy
- **If later, SCT not appropriate**
 - Focus switches to symptom management
- **In the US: some states include x-ALD on their Newborn Screening Panel**

Patient MT

- Transferred to a local hospice for palliative care
- Died end-July 2024, 5 months after initial presentation
- Genetic result mid-July 2024

REPORT SUMMARY:

Hemizygous for a pathogenic variant in the ABCD1 gene.

This result is consistent with a genetic diagnosis of x-linked adrenoleukodystrophy.

Multidisciplinary approach

Medical teams involved:

- Neurologist
- Neurosurgery
- Neuroradiology
- Neuropathology
- Electron Microscopy
- Metabolic Medicine
- Clinical Biochemistry
- Endocrinology
- National Inherited White Matter Disorder Services
- Palliative Care
- Clinical Genetics

Countless Allied Health Professionals

Acknowledgements & References

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Dr. Priya Shanmugarajah, Consultant Neurologist, STH NHS Foundation Trust

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