

EANS/UEMS European examination in neurosurgery

Variants of questions with answers (compilation - Vyacheslav S. Botev,
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Neuropathology

Questions

1. Basics

Cell Types

1. What features do neurons generally have in common?
2. Which kinds of neurons are globular in shape, and which kinds are more trapezoidal?
3. How are granular cell neurons different?
4. Where are they commonly found?
5. What changes are indicative of irreversible neuron death?
6. What is ferrugination?
7. Give three examples of progressive or reversible neuronal injury.
8. When does central chromatolysis occur?
9. What changes are seen histologically?
10. What is neuropil?
11. What comprises neurofibrillary tangles?
12. Is the brain predominately composed of glial cells or neurons?
13. What is the purpose of microglia?
14. How can microgliosis be detected?
15. How might mildly injured microglia appear histologically?
16. Which cells are classified as macroglia?
17. What are the two main kinds of astrocytes, and where are they located?
18. Which histological changes are seen in reactive astrocytosis?
19. What are gemistocytic astrocytes?
20. In chronic reactive astrocytosis, what is the name of the “flame-shaped” proteinaceous accumulations that are typically found?
21. What is piloid gliosis?
22. What is Chaslin’s gliosis?
23. What are Alzheimer type II astrocytes?
24. From what do they result?
25. Where are they found?
26. What kind of reactive astrocytes appear to have many tiny nuclei?
27. When would tissue repair *not* result in gliosis?

28. Can gliosis occur in utero?
29. Where are ependymal cells located?
30. What clinically insignificant sign of “imperfect development” may be found along the lateral ventricles?
31. How does the central canal of the spine change as children become adults?
32. What is another sign of aging ependymal cells?
33. How does the choroid plexus differ microscopically from the rest of the ependyma?
34. How much CSF ultrafiltrate is produced by these cells on a daily basis?
35. True or false: Oligodendrocytes are more common in gray matter than white matter.
36. What is the embryological precursor of melanocytes?
37. Where are melanocytes most prevalent?
38. Are leptomeningeal melanocytes more similar to dermal melanocytes or the melanin-producing cells of the substantia nigra?
39. What are arachnoid cap cells?
40. What can give meningotheial cells the appearance of central clearing?
41. What are the differences between primary and secondary glioblastoma?
42. What are Antoni A and Antoni B areas?
43. Other than schwannomas, which other tumor may show a dual histologic pattern?
44. Which bone tumors have giant cells?
45. Histologically, what is the name given to the cell that are seen in chordomas?
46. Which neoplasm is characterized by the Reed-Sternberg binucleated cells?

2. Rosettes

1. What are rosettes?
2. What are pseudorosettes?
3. What do they indicate?
4. What is the difference between a Homer Wright (HW) rosette and a Flexner-Wintersteiner (FW) rosette?

3. “Body Building”

1. What are Marinesco bodies?
2. When and where are they seen?
3. What are Negri bodies?
4. Where are they seen?
5. What other focal microglia collection may be seen with rabies?

6. What are Hirano bodies?
7. When and where are they seen?
8. What are Lewy bodies?
9. Where and when are they seen?
10. What are pale bodies?
11. What are Pick bodies?
12. Where and when are they seen?
13. And Bunina bodies?
14. What are Verocay bodies?

4. Stains

1. What is the standard general histology stain used for microscopic examination?
2. When could the H&E stain demonstrate astrocytes?
3. What major cellular structure is stained blue-purple by the H&E stain?
4. What is the mechanism by which this occurs?
5. What other structure may appear blue-purple (amphophilic)?
6. What does the eosin stain do?
7. Which cellular structures typically appear pink?
8. With what other histological processing technique is the H&E stain incompatible?
9. How is hematoxylin alone used in other histology techniques?
10. Which other stains effectively show neurons?
11. How does a Nissl stain work?
12. How can astrocytes be best demonstrated?
13. Which of these are useful specifically for fibrillary astrocytes?
14. What does Luxol fast blue stain?
15. Can Luxol fast blue (LFB) help identify neuronal migration defects?
16. Name three other myelin stains.
17. What are two traditional silver staining methods that may detect neurofibrillary pathology?
18. Which of these may help identify about twice as many neurofibrillary tangles (NFTs) in Alzheimer's?
19. Which silver impregnation methods may differentiate Pick bodies from Alzheimer's neurofibrillary tangles?
20. How can silver stain identify CNS injury common in patients who require chronic hemodialysis?
21. When can silver stain help identify diffuse axonal injury (DAI)?
22. Name two stains that can be used to identify amyloid.

23. With polarizing illumination, how would you expect an amyloid deposits stained with Congo red to appear?
24. Which lipid storage disease results in PAS-positive cells that may contain multiple nuclei?
25. Biopsy of the sural nerve in which leukodystrophy demonstrates accumulation of sulfatides (identified with acidified cresyl violet/toluidine blue O on frozen sections) in macrophages?
26. What would PAS show in Andersen's disease (the glycogen storage disorder with "branching enzyme" deficiency)?
27. Which other structures may the PAS be used to identify?
28. How else might you identify fungi?
29. What stain is useful to identify Cryptococcus in CSF?
30. Name three stains that can be used to identify acid-fast bacilli, including Mycobacteria and Nocardia.
31. Which stain could be used to visualize hemosiderin deposits and iron mineralization?
32. Which stain could be used to visualize calcium mineralization?
33. What does the Fontana-Masson stain identify?
34. Which stain is useful for identifying pericellular deposition of collagen?
35. Which collagen/fibrin stain is commonly used to identify fibrosis?
36. How does the Van Gieson stain help in evaluating vascular malformations?
37. Which stain can identify lipid globules near necrotic capillaries after fat embolism?
38. Which staining is positive in schwannoma?
39. S-100 staining is positive in which tumors?

5. Stains: Recap

1. What stain highlights amyloid and/or senile plaques?
2. What stain highlights Lewy bodies?
3. What stain highlights macrophages?
4. What stain highlights neurosecretory granules?
5. What stain highlights astrocytes?
6. What stain highlights toxoplasma?
7. What stain highlights myelin?
8. What stain highlights fungi?
9. What stain highlights neurons and/or neurites?
10. What stain highlights nerve cell bodies?
11. What stain highlights glycogen and basement membrane?
12. What does S-100 stain highlight?

13. What stain highlights glial and neuronal inclusions?
14. What does MIB-1 stain highlight?

6. Immunohistochemistry

1. What are the three major antibodies used to tag neurons?
2. What does NeuN identify?
3. Which neuronal nuclei cannot be identified with the NeuN antibody?
4. What is synaptophysin used to identify?
5. What is the downside of using synaptophysin?
6. Which macroglia is synaptophysin negative?
7. Why can antibody to neurofilament be used to identify neurons?
8. How can neurofilament antibodies differentiate between the cell body and its processes?
9. Which antibody can tag fibrous astrocytes?
10. Can protoplasmic astrocytes also be identified with GFAP antibody?
11. What about reactive astrocytes?
12. And ependyma?
13. Which immunostain can reliably differentiate oligodendrocytes from astrocytes?
14. Which immunostains are used to identify microglia?
15. What is the most sensitive way to identify cerebral amyloid angiopathy?
16. Is silver stain or anti-A β amyloid immunostaining more sensitive for detecting plaques in Alzheimer's disease?
17. What other antibody may detect features of Alzheimer's?
18. How can the inclusion bodies of amyotrophic lateral sclerosis (ALS) best be identified?
19. Is ubiquitin immunostaining useful for Huntington's disease, as well?
20. What about Pick's disease?
21. For which other neurodegenerative disorders is ubiquitin immunostaining of the substantia nigra a sensitive means of detection?
22. How are these disorders differentiated?
23. What is a more sensitive and specific antibody for detection for Lewy bodies?
24. Do NFTs react with α -synuclein?
25. Do the oligodendroglial coiled bodies of corticobasal degeneration (CBD) react with α -synuclein?
26. What antibody is widely immunoreactive in CBD to identify neuronal cytoplasm, astrocytic plaques, and tangles?
27. Are the ballooned neurons in CBD immunoreactive with ubiquitin?

28. Which antibodies can more consistently identify these neurons?
29. In what pediatric disease would immunohistochemistry be used to identify abnormal osteoblasts?
30. Which are the specific immunohistochemical markers for melanoma?
31. Which are the two common positive immunohistochemical stains in meningiomas?
32. Name immunohistochemical markers used in the diagnosis of germinoma.

7. Parkinson's

1. Must Lewy bodies be present for a diagnosis of Parkinson's disease?
2. Where are they typically found in Parkinson's disease?
3. What other microscopic finding is characteristic of Parkinson's?
4. What reactive changes might be seen as a result of this neuronal loss?
5. Is there a familial component to Parkinson's?

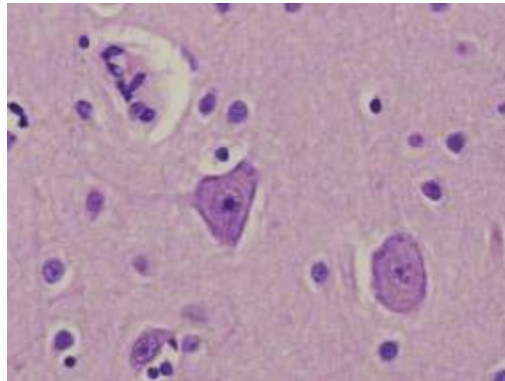
Neuropathology

Answers

1. Basics

Cell Types

1. Round nucleus with prominent nucleolus and soma with lots of rough ER (Nissl substance)



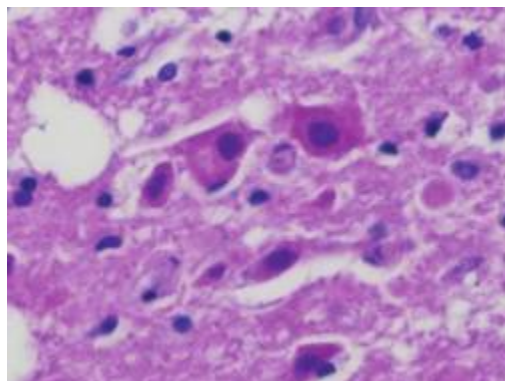
Pyramidal neurons have round nuclei with a prominent nucleolus. The soma is pink-purple (amphophilic), due to abundant rough endoplasmic reticulum (Nissl substance). Motor neurons are trapezoidal, whereas sensory neurons are globular. The background neurophil is homogeneous, and the cell bodies of resting astrocytes cannot be seen.

2. Sensory are globular, and motor are trapezoidal.

3. They are much smaller and do not always show cell processes in normal sections.

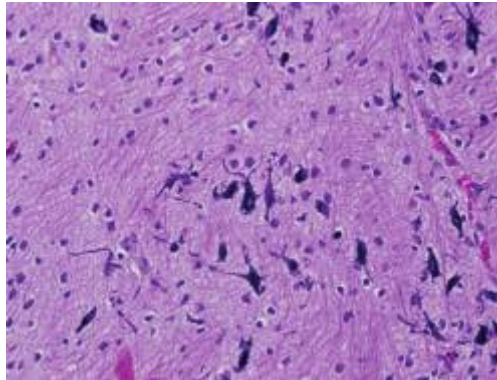
4. Commonly found in the cerebellum and dentate gyrus of hippocampus

5. “Red is dead”: The neuron shrinks; the basophilic cytoplasm becomes eosinophilic; the nucleus becomes dark and shrunken, with loss of nuclear detail (pyknosis); occurs within 6 hours of ischemic necrosis.



Irreversibly damaged “red neurons” are shrunken. The normally basophilic cytoplasm becomes eosinophilic. The nucleus is pyknotic, with shrinking, hyperchromasia, and loss of nuclear detail.

6. The coating of dead neurons with Fe^{2+} and Ca^{2+} salts.



Dead, ferruginated neurons are coated with Fe^{2+} and Ca^{2+} salts.

7.

1. Central chromatolysis
2. Neurofibrillary tangles
3. Neuronal storage of lipid or carbohydrates.

8. After axonal injury.

9. Nissl substance disappears, soma enlarges, and the nucleus becomes eccentric.

10. Axons, dendrites, and glia in gray matter in between neuronal cell bodies.

11. Hyperphosphorylated tau, neurofilaments, and actin.

12. Glial cells (10 to 50 times more numerous than neurons; 90% of all CNS cells are glia).

13. Microglia are antigen-presenting cells (monocyte/macrophage lineage) important in responding to microbial organisms.

14. Increased expression of major histocompatibility complex classes I and II (detect by immunohistochemistry).

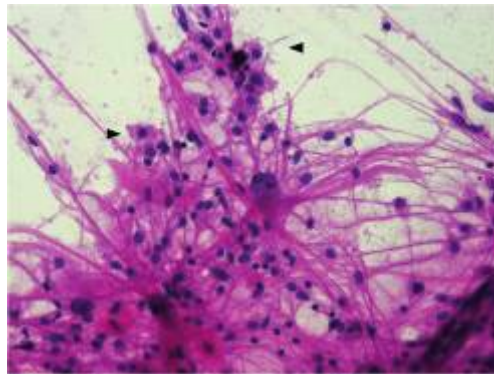
15. Rod cells with enlarged, cigar-shaped nuclei.

16. Astrocytes, ependyma (including choroid plexus), and oligodendrocytes.

17.

1. Fibrillary, mostly in white matter
2. Protoplasmic, predominately in gray matter.

18. Both proliferation and hypertrophy.



The reactive astrocytes, as seen in this cytological smear preparation, show eosinophilic cytoplasm and abundant cytoplasmic processes. Macrophages can also be readily identified on cytological preparations (arrowheads).

19. Reactive astrocytes: swollen but functional, with a large, eosinophilic cytoplasm and (often) eccentric nucleus.

20. Rosenthal fibers.

They are brightly eosinophilic bodies, measuring 10 to 40 μm , with heterogeneous shapes. Their immunohistochemistry shows; peripheral labeling by GFAP, ubiquitin, and $\alpha\beta$ -crystallin; the central hyaline core does not show this labeling. They can be seen in a variety of conditions. They can be found within neoplasms, such as within juvenile pilocytic astrocytomas (JPAs), around craniopharyngiomas and multiple sclerosis plaques, and in neurologic conditions such as Alexander disease.

21. Another form of chronic reactive astrocytosis: elongated astrocytes with bipolar processes form areas of dense gliosis, mimicking pilocytic astrocytoma.

22. Dense interface or subpial gliosis seen in patients with chronic epilepsy.

23. Metabolic reactive astrocytes. They are protoplasmic astrocytes that have large vesicular nuclei with peripheral chromatin, little cytoplasm, and minimal GFAP immunostain-positive processes.

24. Acute hepatic encephalopathy, Wilson's disease, and Canavan/Bertrand disease.

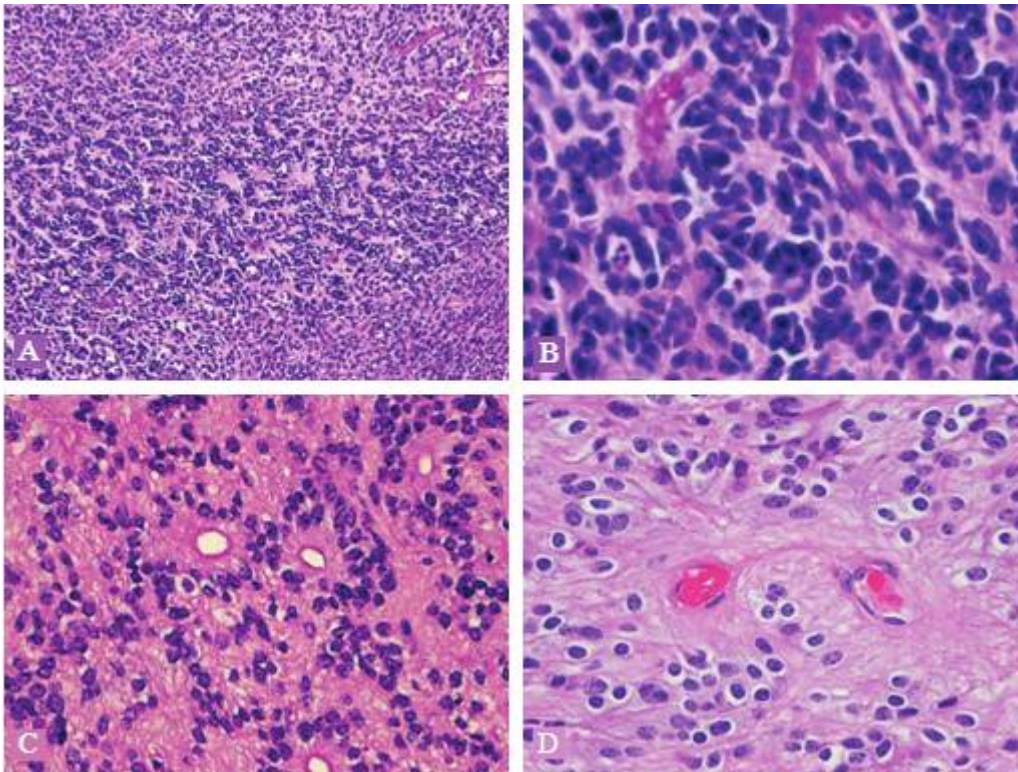
25. Cerebral cortex, basal ganglia, and brainstem.
26. Creutzfeldt cells, which are multinucleated with abundant cytoplasm and microgranular mitoses; associated with demyelinating disease.
27. During the first 20 weeks of gestation in a fetus' CNS.
28. Yes, after 20 weeks' gestation, injuries result in copious gliosis.
29. Along the lining of the ventricular system (single-layer).
30. Ependymal outpouchings or canals, more common in the posterior portion.
31. In childhood, the central canal is lined by ependyma and serves as a channel for CSF. In adults, the canal is collapsed.
32. Gradual loss of cilia.
33. Microvilli from the apical surface; larger, cobblestone-shaped cell bodies and smaller nuclei.
34. 400 to 500 mL
35. False; since they are the CNS's myelinating cells, they are more common in white matter.
36. Neural crest cells.
37. Base of the brain, brainstem, and ventral portion of the upper cervical spinal cord.
38. Dermal melanocytes, because the melanin is made in cytoplasmic melanosomes.
39. Clusters of meningotheial cells at the tips of arachnoid granulations.
40. Their oval nuclei with dispersed chromatin may have intranuclear cytoplasmic invaginations (pseudoinclusions).

41. Primary GBM develops in older patients (55 years) and is slightly more common in men. They usually have EGFR (epidermal growth factor receptor) overexpression, PTEN (phosphatase and tensin homolog) mutations, CDKN2A (cyclin-dependent kinase inhibitor 2A) (p16) deletions, and less frequently, MDM2 (murine double minute 2) amplification.
Secondary GBM develops in younger patients (39 years), and is slightly more common in women. Two thirds of patients have TP53 mutations and no EGFR amplification.

42. Antoni A is an area of dense histologic patterns and Antoni B is an area of loose histologic patterns in schwannomas.
43. Pilocytic astrocytoma
44. Aneurysmal bone cyst and giant cell tumor.
45. Physaliphorous or "bubble-bearing" cell.
46. Hodgkin lymphoma. About 20% of these patients develop neurologic complications involving the skull or meninges.

2. Rosettes

1. A spoke-like arrangement of cells around a central core. A true rosette is formed as the inherent growth pattern of a tumor. The centers appear empty or have cytoplasmic processes.



(A) An area with many Homer Wright rosettes in a PNET. (B) Homer Wright rosettes show a spoke-like arrangement of cells around a central meshwork of fibers. (C) Ependymal rosettes recapitulate ependymal canals, with a central lumen. (D) A perivascular pseudorosette, with a central blood vessel.

2. A rosette whose central canal is not formed by the tumor cells, but by native, nonneoplastic elements (e.g., a blood vessel in the case of a perivascular pseudorosette).

3. Though not pathognomonic for any specific tumor, they aid in understanding tumor differentiation.

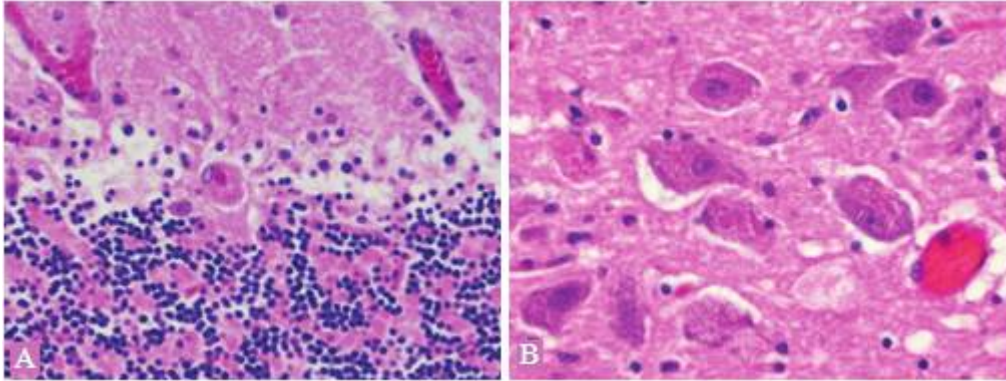
4. HW rosettes have central meshworks of fibers, whereas the centers of FW rosettes are empty.

3. “Body Building”

1. Neuronal intranuclear eosinophilic inclusions containing ubiquitin.

2. They may be seen in normal brain, predominantly seen in the substantia nigra and locus ceruleus. They increase in an age-dependent fashion and are markedly elevated in dementia with Lewy bodies.

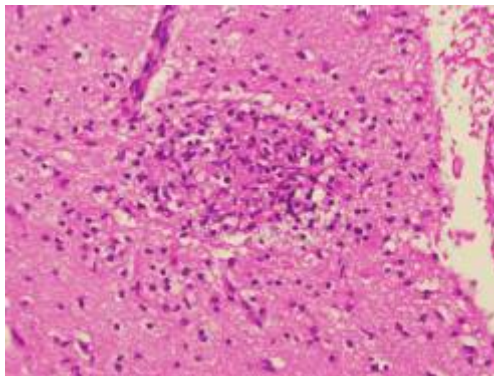
3. Neuronal cytoplasmic eosinophilic inclusions that result from rabies virus infection (look like red blood cells).



Negri bodies can be seen in (A) Purkinje cells and in (B) pyramidal neurons.

4. Best seen in Purkinje cells, pyramidal cells of the hippocampus, and brainstem nuclei, but may be identified throughout the CNS

5. Babès' nodules.



A microglial nodule.

6. Neuronal cytoplasmic cigar-shaped eosinophilic inclusions, composed of actin and related proteins.

7. Particularly in Alzheimer's and Pick's diseases: in CA1 hippocampal neurons.

8. Neuronal cytoplasmic spherical inclusions (8 to 30 μm in diameter) with a pale halo surrounding a hyaline eosinophilic core; predominantly composed of α -synuclein, ubiquitin, neurofilament proteins, and αB -crystallin.

9. In Parkinson's disease: predominantly in the substantia nigra and locus ceruleus.

In dementia with Lewy bodies: predominantly in the cerebral cortex as well as the substantia nigra

10. Neuronal cytoplasmic granular pale Eosinophilic bodies that lack the halo of classic Lewy bodies; they are found near Lewy bodies and have a similar immunohistochemical profile; thought to be either Lewy body precursors or structures that develop in parallel.

11. Neuronal cytoplasmic spherical mildly basophilic inclusions. Unlike Lewy bodies, they do not have a halo; predominantly composed of phosphorylated neurofilament, tau protein, and ubiquitin.

12. In Pick's disease: within pyramidal neurons and dentate granule cells in the hippocampus, as well as within involved areas of the cerebral cortex (usually in the frontal and temporal lobes).

13. Neuronal cytoplasmic round eosinophilic inclusions (2 to 4- μ m diameter); found in the anterior horns of approximately 80% of ALS patients; considered to originate from the ER and are immunolabeled with antibodies against cystatin C

14. Verocay bodies are typically densely packed whorled arrangements in palisaded cells of Antoni A areas of schwannomas.

4. Stains

1. Hematoxylin and eosin (H&E).

2. Reactive astrocytes show eosinophilic cytoplasm and an increase in cell processes, which can be stained by H&E.

3. Nucleus.

4. Hematoxylin, a basic metal-dye complex, binds to nucleic acids (DNA).

5. Cytoplasm, when many polyribosomes are present, due to increased nucleic acids (RNA).

6. Eosin is an acidic dye; it binds to basic/negatively charged structures, such as cationic amino groups on proteins.

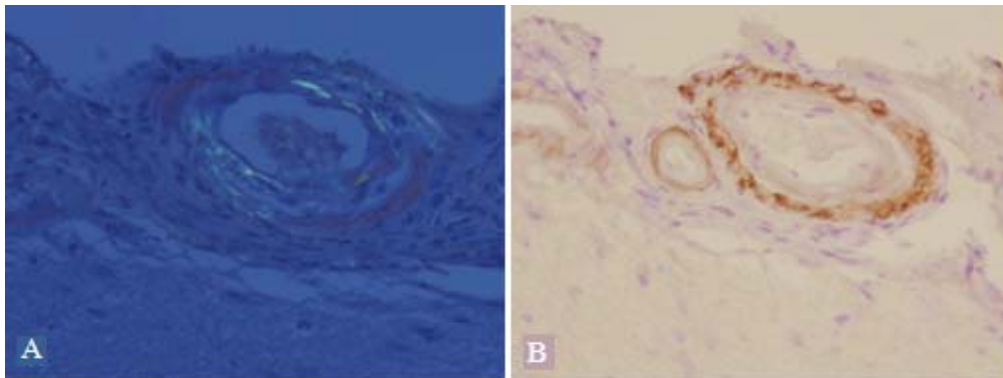
7. Cytoplasm, extracellular matrix.

8. Immunofluorescence

9. As a counterstain in immunohistochemistry and in-situ hybridization procedures.

10. Nissl stain and heavy metal impregnation techniques.

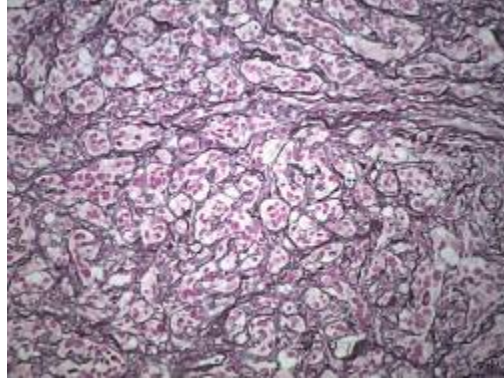
11. Nissl stain is basic; binds to DNA in nucleus and RNA granules in soma (Nissl substance).
12. Holzer stain, phosphotungstic acid-hematoxylin stain, heavy metal (silver) impregnation techniques, and immunostain for GFAP intermediate filament.
13. Silver stains and GFAP immunostain.
14. Myelin
15. Yes: LFB helps highlight heterotopic gray matter within white matter tracts in neuronal migration defects.
16. Marchi, Sudan, Weigert.
17. Bielschowsky and Bodian.
18. Bielschowsky
19. Gallyas (GAL) for 4R tau and Campbell-Switzer (CS) for 3R tau
Pick bodies: CS+/GAL-
Alzheimer's NFTs: CS+/GAL+
20. Reveal aluminum deposits in the choroid epithelium, neurons, and glia.
21. Axonal swellings containing neurofilament proteins and ubiquitin develop 24 hours and 2 months postinjury, and can be identified with silver stains.
22. Congo red and thioflavin S.
23. Apple-green birefringence.



(A) Blood vessels with amyloid deposition show characteristic apple-green birefringence under polarized light with the Congo red stain. (B) Immunostain for A β -amyloid protein highlights vascular amyloid deposition in cerebral amyloid angiopathy (CAA).

24. Gaucher's disease.
25. Metachromatic leukodystrophy (MLD); cells with sulfatide deposition show brown metachromasia.
26. PAS-positive polysaccharide granules in muscle and skin.
27. Basement membrane, mucopolysaccharides, fungus, corpora amylacea.
28. Gomori's methenamine silver (GMS) and Grocott's methenamine silver stain for Cryptococcus, Coccidioides, Aspergillus, etc.

29. India ink.
30. Fite's, Kinyoun, Ziehl-Neelsen. Mnemonic: "FIT, KIND, ZEALOUS".
31. Perl's Prussian blue stain for iron.
32. Von Kossa.
33. Melanin (leptomeningeal melanocytes and melanotic neoplasms).
34. Reticulin



The pattern of collagen deposition is highlighted by the reticulin stain.

35. Trichrome
36. Vascular elastic lamina are stained; can be used to identify AVMs
37. Oil red O.
38. S-100, Leu 7, laminin, vimentin, and collagen IV.
39.
 - Schwannoma
 - Eosinophilic granuloma
 - Paraganglioma
 - Hemangioblastoma
 - Chordoma
 - Esthesioneuroblastoma
 - Meningioma (20% of the time).

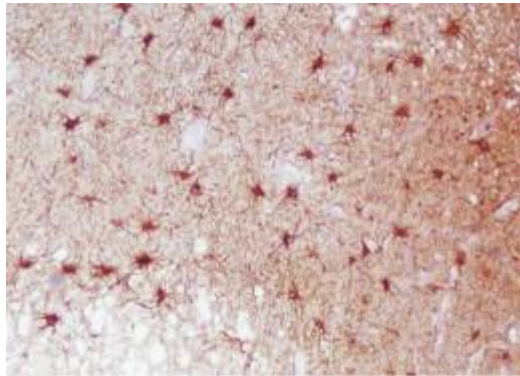
5. Stains: Recap

1. A- β amyloid, congo red, thioflavin S.
2. α -Synuclein
3. CD68
4. Chromogranin
5. GFAP (glial fibrillary acidic protein)
6. Giemsa
7. Myelin basic protein, Loyez.
8. Methenamine silver.
9. Neurofilament protein, synaptophysin.
10. Nissl stain.

11. PAS (periodic acid Schiff)
12. Glia and Schwann cells.
13. Ubiquitin
14. Cells in growth phase of cell cycle (highlights cell proliferation).

6. Immunohistochemistry

1. NeuN, Synaptophysin, Neurofilament.
2. **Neuronal nuclei.**
3. Sympathetic chain ganglia, the internal nuclear layer of the retina, and Purkinje cells.
4. Neuronal presynaptic vesicles.
5. Lots of background from normal cells, so it is difficult to distinguish abnormal neuronal cells or infiltrative lesions.
6. Choroid plexus ependyma
Mnemonic: “Too wet for synapses”.
7. Because neurofilament is the intermediate filament of neurons.
8. Cell bodies have nonphosphorylated neurofilament; **p**rocesses have **p**hosphorylated.
9. Glial fibrillary acidic protein (GFAP), an intermediate filament.
10. Not with routine staining methods; protoplasmic astrocytes contain little GFAP.
11. Yes; GFAP is very effective for demonstrating reactive astrocytes.



GFAP immunostain highlights evenly distributed reactive astrocytes.

12. Weakly GFAP positive.
13. Trick question: unfortunately, none!
14. CD68 and CD163.
15. Anti-A β amyloid immunostaining.
16. Anti-A β amyloid immunostaining (after pretreatment with formic acid).
17. Paired helical filament (PHF) tau antibodies detect neurofibrillary tangles (NFT).
18. Ubiquitin and TDP-43 immunostaining.

19. Yes; abnormal neurites in the cerebral cortex stain positive for ubiquitin.
20. Yes; ubiquitin, neurofilament, and phosphorylated tau protein compose Pick bodies.
21. Parkinson's disease (by identifying Lewy bodies) and dementia with Lewy bodies.
22. Dementia with Lewy bodies has cortical Lewy bodies in addition to those in the substantia nigra.
23. α -synuclein
24. No
25. No
26. Tau
27. Only inconsistently.
28. α B-crystallin and phosphorylated neurofilament.
29. Craniosynostosis
30. MART-1 and HMB-45.
31. Ethidium monoazide (EMA) and vimentin.
32. Placental alkaline phosphatase (PLAP) and c-Kit.

7. Parkinson's

1. Yes; neuronal loss alone is insufficient.
2. Substantia nigra, locus ceruleus, dorsal motor nucleus of vagus, and nucleus basalis of Meynert.
3. Loss of the tyrosine hydroxylase-immunoreactive neuromelanin-containing neurons of the substantia nigra (dopaminergic denervation of striatum), which occurs in a ventrolateral to dorsomedial direction.
4. "Pigment incontinence," which is free melanin in the neuropil or in macrophages, and reactive astrocytosis.
5. Most cases are sporadic, but mutations in chromosome 4 may lead to an autosomal dominant form of the disease and mutations on chromosome 6, an autosomal recessive form.