Introduction to Neuropathology

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Several characteristics of the nervous system make its reactions to trauma and disease unique: it is contained by the bony skull and spinal column, restricting its expansion; the brain is bathed in cerebrospinal fluid (CSF) but a conventional lymphatic system is lacking; immunologic surveillance is limited; and the healing response of neural tissue to injury is different from that seen in the rest of the body. The goal of this talk is to give an overview of cellular components and pathologic processes in the CNS, highlighting those that are particularly unique or medically important. Specifically, I will discuss:

1) Cellular components of the CNS
2) Pathology of neurons
3) Pathology of glia
4) The basic microscopic appearance of infection, trauma, infarction and neoplasia in the CNS

Many of the disease entities I will introduce, such as Stroke and Alzheimer’s disease, are quite Common. Others, such as brain tumors and most infections, are rarer but often Catastrophic. Finally, I will attempt to Clarify some of the basic pathological responses of the brain to disease.

CNS Cellular Components

Neurons
The brain contains about $10^{11}$ neurons. Many different types of neurons exist (sensory, motor, autonomic). Their functional specificities result from differences in morphology, neuronal interconnections, neurotransmitter type, metabolic and electrical activities etc. As will be discussed later, these differences result in selective vulnerability of some neurons to hypoxia, neurodegenerative disease and other pathological insults. In general, neurons have abundant cytoplasm and a large round nucleus with a prominent nucleolus; numerous dendrites and a single axon project from the cell body. The basic reactions of neurons to injury include (1) the acute neuronal injury “red neurons” seen soon after hypoxia/ischemic, toxic or infectious insults, (2) neuronal atrophy/degeneration in chronic disease, (3) Axonal reactions, and (4) neuronal inclusions. The development of silver stains by C. Golgi enabled anatomists and pathologists to visualize neuronal processes. Today, we generally use
immunohistochemical techniques to identify neurons. Specific antibodies recognize neuronal synaptic proteins (synaptophysin), nuclear antigens (NeuN), or neuron-specific filaments (SM31, SM32).

**Glia**
Glia support neurons and their processes and modulate many functions in the brain. They are the most numerous cells in the CNS. The metallic impregnation techniques previously used to identify glia have largely been replaced by immunohistochemical stains, the most common of which is glial fibrillary acidic protein (GFAP). Several different specialized types of glia exist:

**Astrocytes** are found throughout the neuroaxis. They have round to oval nuclei, and take their name from their numerous star-like processes. Traditionally, they have been divided into protoplasmic astrocytes found mainly in the grey matter, and fibrous astrocytes present in both grey and white matter. Astrocytic end-foot processes with tight junctions contact the basal lamina of vessels and of the pia, contributing to the blood-brain and CSF-brain barriers. Astrocytes act as metabolic buffers, detoxifiers, suppliers of nutrients, electrical insulators, and physical barriers. Finally, unlike the rest of the body, where fibroblasts play the major role in scar formation, in the CNS astrocytes play the major role in damage repair.

**Oligodendroglia** are found in the white matter, where their processes wrap around and insulate axons, permitting saltatory conduction. One oligodendroglial cell wraps processes around several axons. Oligodendroglia are characterized morphologically by their round, regular, lymphocyte-like nuclei.

**Ependymal** cells are specialized glia that line the ventricles. They form a continuous layer of single cuboidal or columnar cells with cilia and microvilli at their apical, ventricular surfaces. In addition to providing a barrier between the brain the CSF, ependymal cells are thought to function in secretion, absorption and transport of numerous molecules. The Choroid Plexus is a specialized ependymal organ made up of papillary folds of CSF-secreting ependymal cells protruding into the ventricles.

**Microglia**
These are not really glia, rather, they are bone marrow derived and function as antigen-presenting monocytes in CNS. They are small, elongated cells with a few branched processes. Microglia are uniformly distributed in grey and white matter and are mitotically stable. Like other peripheral monocytes/macrophages, they express MHC I
and II antigens and function in immune surveillance. They respond to injury or infection by transforming into motile, phagocytic cells. In viral diseases one often sees groups of these cells (microglial nodules). They can also be seen clustered around dying neurons in some conditions (neuronophagia).

**Meninges**
The meninges – dura, arachnoid and pia mater – enclose the brain and spinal cord. The dura (pachymeninges) is a dense, fibrous connective tissue that is closely associated with the periostium in the skull. In the spine an epidural space is present. The arachnoid and pia mater together form the leptomeninges, with the outer arachnoid only loosely attached to the dura. The arachnoid matter contains outer subdural and inner mesothelial layers as well as a central layer featuring desmosomes and intercellular tight junctions that limit diffusion. Arachnoid mater drapes loosely over the brain and does not enter sulci. The subarachnoid space between arachnoid and pia contains blood vessels covered by fine arachnoid trabeculae that are continuous with the pia. Pia mater reflects into the cerebral sulci and also covers arteries as they penetrate into the brain. Arachnoid cells form small aggregates called “arachnoid granulations” which are particularly frequent near the intracranial venous sinuses. These granulations protrude into the sinuses, forming arachnoid villi through which CSF is transferred into the sinuses via one-way valves.

**Pathology of Neurons**
**Apoptotic Neuronal Cell Death** or “programmed cell death” is used during normal development to eliminate excess neurons. Apoptotic cells can be recognized morphologically by their characteristic clumped, fragmented chromatin. The controlled fragmentation of the DNA can be confirmed in apoptotic cells using terminal transferase mediated nick-end labeling (TUNEL) staining. Apoptosis can also be the cause of neuronal, lymphoid and glial cell death in CNS disease processes. In contrast to the large clusters of dead cells seen with necrosis, apoptotic cell death tends to strike individual cells in a dispersed fashion.

**Acute neuronal injury** resulting in necrotic cell death can occur due to many causes, the most common of which is hypoxia/ischemia. The initial histologic changes associated with hypoxia include shrinkage of the cell body with increased cytoplasmic acidophilia “red neurons”, and condensation of the nuclear chromatin/pyknosis. Later, nuclear chromatin will also become acidophilic as it degrades and the nuclei will appear to “drop out”. Identical acute changes can also been seen due to hypoglycemia or
exposure to toxins. In adults, the pyramidal neurons of the CA1 field of the hippocampus and layers 3 and 5 of the cortex are especially vulnerable to hypoxic damage, as are purkinje cells in the cerebellum.

Chronic neuronal atrophy/degeneration, such as occurs in neurodegenerative diseases, generally results in gradual neuronal loss without the “red neurons” seen following hypoxic damage.

Axonal Pathologies include axonal degeneration following neuronal cell death and axon reaction. When neurons are killed by infarction or other processes their axons degenerate. This can be useful diagnostically. For example, degeneration of the crossed and uncrossed corticospinal tracts as evidenced by loss of normal architecture and accumulation of CD68-positive macrophages is often used to infer the death of upper motor neurons in ALS. The “axon reaction” is a set of stereotypical morphological and biochemical changes in the neuronal cell body following axonal damage. They include retraction of dendrites, cellular swelling and dispersion of Nissl bodies (chromatolysis), and accumulation of intermediate filaments. In the PNS, but not in the CNS, axonal regeneration and restoration of normal neuronal morphology can occur. A final neuropathologic process involving axons is their demyelination, most commonly in the context of an autoimmune disease such as multiple sclerosis. CNS demyelination results in a very cellular “plaque” made up of foamy lipid-filled macrophages, lymphoid cells and reactive astrocytes. Occasionally the high cellularity and cellular pleomorphism of solitary plaques results in their being misdiagnosed as neoplastic processes.

Neuronal inclusions can occur “normally” during aging or be associated with specific pathologies. Intranuclear Marinesco bodies are seen in otherwise normal neurons in the substantia nigra. Viral infections such as CMV often produce distinctive neuronal nuclear inclusions. Neuronal cytoplasmic inclusions are also seen in neurodegenerative conditions such as Parkinson’s and Alzheimer’s diseases.

Pathology of Glia
Glial cells play a crucial role in the nervous system. Even under normal circumstances, some degree of gliosis (i.e., reactive gliosis) is a common occurrence and can be observed in various pathological conditions, including brain injuries, infections, degenerative diseases, and tumors. Here are some key points about glial cells and gliosis:

- **Gliosis** occurs in a number of different settings and is relatively non-specific. Causes of gliosis include physical or ischemic damage, abnormal electrical activity, infection and autoimmune attack. Some low-grade glial tumors also resemble reactive or gliotic brain tissue. The cytoplasm of reactive astrocytes becomes swollen and more eosinophilic with better-delineated cell borders and processes. Immunohistochemical stains reveal increased production of the intermediate filament protein GFAP in the reactive cells.

- Several more specialized types of glial reaction also exist. For example, in Wilson’s disease and chronic hepatic encephalopathy “Alzheimer type 2” astrocytes with swollen nuclei are seen. “Rosenthal fibers”, glial cytoplasmic filamentous inclusions that appear on H&E stained sections as brightly eosinophilic carrot-shaped or corkscrew-like structures are even more common. These distinctive structures are present in association with longstanding gliosis as is seen around cavities in the CNS, in low grade, discrete astrocytomas such as pilocytic astrocytomas, and in patients suffering from Alexander’s disease, a genetic disorder affecting GFAP.
Glial inclusions are present in both infectious diseases and neurodegenerative conditions. Examples include the amorphous oligodendroglial nuclear inclusions (JC virus) in progressive multifocal leukoencephalopathy (PML) and the glial filamentous cytoplasmic inclusions of progressive supranuclear palsy (PSP).

**Overview of Basic CNS Pathology**

In this final section I want to give you a brief overview of the types of changes associated with various CNS pathologies. These are generalizations that will not hold true in all individual cases but will give you an idea of the “most common” picture for a given process.

**Viral Infection** – Acute viral infections tend to involve the brain parenchyma (encephalitis). One sees lymphocytic infiltrates around vessels and in the neural tissue as well as rod-shaped activated microglia and small microglial nodules. Chronic viral infections can have varied appearances, one of which (PML) is discussed above.

**Bacterial Infection** – Acute bacterial infections generally cause a purulent meningitis or brain abscess; numerous neutrophils tend to be present.

**Fungal Infection** - Either the brain or meninges can be primarily involved. Some fungal infections cause granulomatous inflammatory responses.

**Demyelinating Disease** – Multiple sclerosis is characterized by sharply circumscribed plaques in which myelin is either gone or within foamy macrophages. Reactive astrocytes and preserved axons are also present.

**Trauma** – Trauma can cause superficial contusions, hemorrhage at any site (epidural, subdural, subarachnoid, intraparenchymal) or frank necrosis. Also important is microscopic damage to nerves known as diffuse axonal injury.

**Neoplasia** – The most common CNS tumors are gliomas that infiltrate through the brain and cannot be fully excise surgically. However, all CNS cell types (glia, neurons, meninges) give rise to tumors.

**Neurodegenerative Diseases** – These diseases affect various populations of cells and have disparate mechanisms, but most are characterized by distinctive inclusions within cells and associated neuronal and/or glial cell loss.