Chapter 13

The Nervous System

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Introduction

Aims and scope of the presentation

There are numerous important neurological diseases in which there are no microscopic let alone macroscopic lesions, but in keeping with the theme of the meeting, the presentation will be based around a selected range of conditions that are common or well known, and in which gross pathological changes are significant in diagnosis. In the course of the discussion of these specific entities, aspects of a more general nature will also be addressed. These notes are summary in nature, there being adequate detail available in standard reference texts and on the web. The accompanying Power Point slideshow however should provide a useful body of complementary visual material.

Since the theme of this meeting is gross pathology, no reference list or bibliography is provided, as the basic information is readily available in standard texts. However a list of websites for visual material will be made available at the meeting.

The pathological conditions to be discussed are:

- Polioencephalomalacia
- Focal Symmetrical Encephalomalacia
- Acute Bacteraemic leptomeningitis
- Acute Bacterial and Mycotic Meningoencephalitis/myelits
- Cerebro-spinal Abscess and Suppuration
- Caprine Lentivirus Myeloencephalitis
- Ovine Foetal Copper Deficiency
- Phalaris poisoning
- Ceroid-lipofuscinosis

Sampling the CNS

The nervous system is the problem child when it comes to necropsy in the field, especially of cattle and other large ruminants. I think most pathologists would agree that there is a high rate of poor sample submission for the CNS. The first problem is getting the brain and/or cord out with a minimum of effort, and without "mooshing" the tissue. Various cunning techniques have been devised but it can still be a chore

and takes practice and a good attitude. The second problem is the need for some very basic neuroanatomical knowledge coupled with an understanding of which clinical signs correlate with certain regions of the brain and cord. Oftentimes diagnostic sweat and toil are negated by the submission of the wrong bits. This problem also puts the onus back on the sampler to be well prepared. With the right understanding and background knowledge, any operator can devise his/her own tricks of various trades to obtain diagnostic samples efficiently and even enjoyably. My advice – use your imagination but make it soundly based. All sorts of tools from angle-grinders to embryotomy wire to axes and tomahawks can with practice be used to good neurodiagnostic effect. Small gashes and slashes don't usually spoil the tissue –squashing and mushing does.

Hot tip - if sampling in the field is a big problem, consider taking heads and spinal segments back to base and working on them there.

Pseudolesions

- Meningeal melanosis
- Meningeal vascular prominence
- Venous sinuses

Polioencephalomalacia (PE)

General

This "disease" is really a reaction pattern following a single episode of acute necrotizing injury to cerebral grey matter. Aetiological factors include thiamine deficiency, thiamine unavailability (including rock fern poisoning), hydrogen sulphide poisoning (cattle) and perhaps others. The pathogenesis probably involves interference with oxidative energy metabolism at sites of high demand.

Distribution and character of the lesions

Typically bilaterally symmetrical and extensive, and classically involving the dorso-lateral cerebral cortex, with involvement of thalamic and brainstem nuclei, particularly the caudal colliculus.

Lesions consistent with this diagnosis will vary in appearance according to their age.

1. In most situations **acute phase** lesions are to be expected, i.e. involving tissue actively undergoing necrosis and removal, and reflecting ischaemia and vascular injury of **one to several days** duration.

2. In a few cases, inactive, end-stage changes will be found i.e. reflecting permanent loss of neural tissue with stable residual cavitations or surface distortions. This takes **weeks to months** to achieve.

3. Sometimes changes will reflect a time course intermediate between acute and end-stage disease.

Acute phase changes

The brain overall is frequently **swollen**, as detected by flattening of cortical gyri and herniation of the cerebellar vermis (through the foramen magnum) and caudal cerebral hemispheres (under the tentorium cerebelli). This may also compress the brainstem dorso-ventrally.

The directly affected tissue is softened, discolored (yellowish) and sometimes haemorrhagic. It is important to remember that **changes may be subtle**. In such cases, transection of the fresh brain and careful inspection may reveal lines of separation where necrotic cortical grey matter cleaves away from adjacent normal tissue.

An additional useful feature is that necrotic tissue will often fluoresce under UV light (Wood's lamp), even when not otherwise conspicuous. This also applies to fixed tissue.

Submission for histologic confirmation should include at least a hemibrain.

End-stage changes

Progression to this stage requires that the animal has survived the initial insult by several weeks or months. Net tissue loss at lesional sites leaves cystic cavities or surface deformities. In many cases these can be subtle, but in some very spectacular.

Focal Symmetrical Encephalomalacia (FSE)

General

This is a tissue lesion that is recognized as a disease-specific diagnosis in sheep when it occurs in the basal forebrain. The cause is the epsilon toxin of Clostridium perfringens type D, and FSE is thus part of the spectrum of classical clostridial enterotoxaemia, being a manifestation of a subacute rather than a peracute form.

Distribution and character of the lesions

Bilaterally symmetrical in the **internal capsule** and often **cerebellar peduncles**. Sometimes there is another pattern involving the subcortical white matter and dorso-lateral thalamus. In contrast to PE it is predominantly a **white matter** lesion.

The lesions are caused by toxic injury to blood vessels at these sites, producing fluid effusion, haemorrhage and ultimately infarction. The gross changes seen are thus somewhat similar to PE in that early

changes involve softening and often haemorrhage in the affected areas. Lesions would cavitate over time, but most animals die in the acute/subacute phase.

It is worth remembering that even if gross changes are not present, the vascular injury is often evident **microscopically** and the submission of brain is very useful for trying to establish a diagnosis of ET, which is often a "garbage bin" diagnosis when ruminants die suddenly and are variably autolysed at necropsy. The brain undergoes PM autolysis relatively slowly and can be a very useful specimen in these circumstances.

Acute Bacteraemic Leptomeningitis

General

The great majority of bacterial infections of the CNS of ruminants are haematogenous, and according the agent involved, may 1) extensively involve both the neuroparenchyma and meninges (see below), or 2) remain largely restricted to either the meninges or parenchyma. The common organisms are coliforms, streptococci and pasteurellae.

Infections whose localization tends to be meningeal, while sparing the parenchyma may however also involve the choroid plexuses and ependymal surfaces of the ventricles. Not infrequently they also involve the serous membranes, joints and eyes (particularly streptococcal infections).

These infections often involve animals in the first days of life, in which case they reflect deficiencies in resistance, such as failure of adequate transfer of colostral antibodies. The organisms involved may not be classical primary pathogens.

In somewhat older animals the organisms may be more typical primary pathogens.

The clinical disease produced is generally acute, severe and rapidly fatal. It may begin with anorexia, pyrexia and drowsiness and progress to diffuse neurologic signs that may include paresis, ataxia, abnormal nystagmus and head tremor. Terminally prostration, opisthotonus and semi-coma supervene. Occasionally there may be seizures.

Distribution and character of lesions

As there is extensive to diffuse acute inflammation of the leptomeninges, varying degrees of leptomeningeal hyperaemia with fibrinous or purulent effusion are expected. Inflammatory exudates gravitate ventrally and accumulate over the ventrum of the brainstem. Dorsally it pools in the cerebral sulci. Inflammatory effusion may give the leptomeninges a grayish to yellowish and thickened opacified appearance.

Considerable swelling of the brain may be in evidence. This can be manifested in various ways – 1) flattening of cerebral gyri, 2) herniation of the cerebellar vermis, 3) herniation of the parahippocampal gyri under the tentorium with dorso-lateral compression of the brainstem.

Transverse sections of the brain may reveal swelling and reddening of choroid plexuses and discoloration and roughening of the ependymal surfaces of the ventricles (and also the compression of the brainstem mentioned above). In animals that survive several days, dilation of the lateral and third ventricles will follow plugging of the aqueduct, and exudate may be found within the ventricles.

As noted above fibrinous to fibrinosuppurative exudates may be found in serous cavities, joints and eyes.

Acute Bacteraemic Meningoencephalitis/myelitis

General

Here we consider those acute haematogenous bacterial infections, which while often involving the meninges, target the parenchyma of the CNS for major injury, albeit indirectly via the production of vasculitis.

The archetype for this pattern of disease is **Bovine Thrombotic Meningoencephalitis (TME)**, caused by septicaemic infection with Hemophilus somnus. It has classically been documented as a disease of lot-fed beef cattle at around a year of age, but can occur in other situations.

Clinical signs are similar to those described above for leptomeningitis.

Distribution and character of the lesions

Septicaemic localization is primarily onto the endothelium of blood vessels in various organs, including the CNS. The resulting underlying disease processes of vasculitis and thrombosis produces haemorrhagic septic infarcts deep within the substance of the brain and spinal cord. These appear as soft red-brown foci from a few millimeters to several centimeters in diameter, which often are concentrated at the junction of grey and white matter, or close to the surface.

Since there is also meningeal localization, hyperaemia, exudation and opacification of the leptomeninges are expected.

The acute, severe and extensive nature of the process will also predispose to the changes associated with brain swelling (see above).

In other organs systems, vasculitis and secondary infarction often occur in the myocardium and skeletal muscles, and fibrinopurulent synovitis and serositis may be seen.

A similar disease but with typically much less spectacular gross lesions in the CNS is **Sporadic Bovine Encephalomyelitis (SBE)**, caused by a strain of Chlamydia spp. Animals 6 months to 1 year of age are most susceptible. Like TME the fundamental process is generalized vasculitis that involves blood vessels throughout the brain and cord. However infarction is on a much smaller scale, probably because smaller vessels are involved, and grossly visible haemorrhages and infarcts are not reported to be common except in unusually florid cases. Some brain swelling may often be appreciable, and this in combination with fibrinous polyserositis would be suggestive findings.

Cerebro-spinal Abscesses/suppuration

General

Here we are highlighting those sporadically occurring, subacute to chronic pyogenic infections that tend to result in one or a few localized suppurating lesions. Organisms commonly implicated are Arcanobacterium pyogenes and Pasteurella sp.

Abscesses involving the CNS are generally either epidural or intramedullary, and the route of infection may be embolic or by extension from an adjacent structure.

Epidural lesions frequently arise via the extension of infection from adjacent skeletal structures, although this itself, particularly in the spinal column, may be haematogenous in origin. Common loci from which extension may occur include the ethmoid, the nasal sinuses, the middle ear, and the vertebral bodies. The infection may be contained and confined by the dura, or may extend to the underlying nervous tissue. Subdural containment is rare.

Intramedullary lesions that are the result of septic thrombo-embolism are usually located in the cerebral cortex at the junction of the grey and white matter, or in the hypothalamus. Large septic emboli are most likely to arise from bacterial endocarditis. Abscesses that result from direct extension will be adjacent to the site from which extension arose. Infections in the nasal and paranasal cavities may extend into the brain via passage through the complex of valveless veins that connect with the dural sinuses. A similar situation can occur in the spinal canal when infections associated with tail docking can track along vertebral venous sinuses.

Distribution of lesions as a guide to pathogenesis

Frontal/olfactory abscess/suppuration suggests extension from the ethmoid or sinuses and may be associated with dehorning wounds, nose rings, fighting wounds in males, nasal bots in sheep,

Superficial cerebral or epidural abscess/suppuration suggests extension from adjacent sinuses or infected calvaria

Deep cerebral or hypothalamic abscess/suppuration suggests septic embolic infection

Pituitary abscess/suppuration suggests infection tracking from the nasal tissues via venous channels.

Cerebello-pontine abscess/suppuration suggests extension from the middle ear/tympanic bulla

Spinal epidural abscess/suppuration when thoraco-lumbar suggests extension from vertebral body osteomyelitis, usually septic embolic, and often located dorsal to the heart or the kidneys. In the lumbo-sacral region it may reflect infection tracking along vertebral venous sinuses from the base of the tail.

Haematogenous Mycotic Meningoencephalitis/myelitis

General

Haematogenous mycotic infections are sporadic events that generally reflect some severe defect of resistance or immunocompetence at any stage of life. This is likely to be severe debility, lack of colostrum, prolonged antibiotic therapy etc. Agents likely to be involved include Aspergillus and Mucor sp. A more specific association occurs in adult cows that abort because of placental infection with the fungus Mortierella wolfii. The process of abortion may result in fungaemia and potential localization in tissues including the CNS.

Character of lesions as a guide to pathogenesis

Because these agents love to invade arterial walls, the character of the lesions is heavily influenced by vasculitis, thrombosis and infarction. Thus large lesions may appear as areas of discoloration and softening or even cavitation.

No particular sites of localization are documented, but it is my impression that the caudal fossa is often the major site in calves and lambs.

Caprine lentivirus (CAEV) myeloencephalitis

General

As part of the disease spectrum associated with the caprine lentivirus, this neurologic disease is mostly encountered in goat kids around 2-4 months of age. The fundamental disease process is an intense, immune-mediated demyelinating inflammatory reaction, and is thus centered on white matter. Severe demyelination may progress to necrosis, mineralization and cavitation over some weeks. Clinically there is acute onset, rapid progression and lack of recovery.

Distribution and character of lesions

Single (sometimes unilateral) or multiple focal lesions are produced predominantly in the caudal brainstem and spinal cord, and clinical signs reflect this fact with upper motor neuron and general proprioceptive deficits predominating. However a range of signs is possible, since focal lesions can extend all the way to the frontal lobes in rare cases.

Acute lesions (less than one week) in the spinal cord consistent with this diagnosis will appear as localized, random, asymmetric areas of dull white to brown discoloration at the periphery, extending from the surface to impinge on the grey matter, and often with considerable associated tissue swelling.

In the caudal brainstem lesions have a similar character and are centered on white matter tracts but may extend to grey nuclei. In the cerebrum focal lesions are often periventricular.

More chronic lesions (one to several weeks) may exhibit softening and even cavitation.

Foetal Copper Deficiency (Swayback)

General

Primary or secondary deficiency of copper in foetal lambs can produce two different clinical entities – congenital "swayback" in the neonate and "enzootic ataxia" in lambs from a few days to several months of age. In the former about half the cases will have gross changes in the cerebral white matter. In the latter, and the remaining 50% of neonates, no gross changes are evident, but degeneration of populations of neurons is detectable microscopically.

In copper deficient foetal goats however, congenital disease and gross cerebral lesions are rarely produced, and delayed-onset disease with microscopic lesions is more typical, often with cerebellar degeneration and marked degeneration of spinal motor neurons and nerves (both rare in lambs)

Distribution and character of lesions

Typically in swayback there is bilateral symmetrical transformation of the white matter throughout the cerebral hemispheres (corona radiata and centrum semiovale) ranging from gelatinous oedema to porencephaly/hydranencephaly. In extreme cases the hemispheres are reduced to a state of collapse when the calvaria is removed. In less severe cases there will be varying degrees of cystic degeneration of white matter and ventricular dilation.

Phalaris Poisoning

General

Neurologic manifestations of phalaris poisoning (Phalaris staggers) may be delayed for weeks after exposure to the plant and grossly visible changes may be in evidence in the CNS in some cases. This is due to the accumulation of a pigment within neurons, leading to the discoloration (sometimes marked) of grey matter. It will also cause a similar discoloration of the renal medulla. This storage lesion is probably an epiphenomenon rather than causally related to the functional deficits, which are thought to be due to serotonin-related phytotoxins. The stored pigments are probably indolic metabolites.

Distribution and character of lesions

Pigment storage occurs throughout the brain, cord and ganglia, and can cause a distinctly greenish discoloration which is universal if severe. If less intense it will be evident in brainstem nuclei, spinal grey matter and dorsal root ganglia.

Ceroid-lipofuscinosis

General

This type of storage disease process centers around the accumulation of lipopigments in neurons to the extent that the color of the fresh brain may be altered. Ovine inherited Ceroid-lipofuscinosis is, as far as the author is aware, documented only in South Hampshire sheep in New Zealand. However in Western Australia neuronal lipofuscinosis has been documented in livestock exposed to the introduced South African pant Trachyandra divaricata. As is the case with Phalaris, the storage process probably has no direct correlation with clinical deficits, but that is not the case with the inherited disease. It should be pointed out that at this point in time, the only thing these two diseases have in common is neuronal pigment storage, and metabolically they may well be (probably are) fundamentally different.

Distribution and character of lesions

In both diseases lipopigment accumulation causes rusty brown discoloration of grey matter. In the case of Trachyandra-associated disease, the pattern is similar to that described for phalaris, except that the kidney is not involved. However, in the genetic disease the storage process is neuronotoxic, and after about four months of age neuronal loss progressively leads to atrophy particularly of the cerebral cortex.