MRI findings in rare and unusual brain diseases - how to approach a case when the MRI is like nothing you have seen before

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1. A framework for solving the puzzle.

All MRI studies should be interpreted in light of the clinical context, but this is of crucial importance when the MRI is unusual or atypical. This often requires a good working relationship between the radiologist and the clinician, with a collaborative approach to solve these challenging cases. The *signalment* can prime the radiologist to consider a number of congenital diseases, either developmental structural defects or inherited errors of metabolism. The *history of onset and natural progression of signs* can also help to indicate if there might be stable anatomic disease or a progressive neurodegenerative disease, for example. And a *detailed neurologic examination* should also be correlated with any MRI findings, and in cases of subtle disease can prompt detailed examination of certain areas of the brain, or the use of special sequences to optimise visualisation of a lesion.

A solid grasp of neuroanatomy is very helpful. In particular, knowledge of smaller cerebral structures, including the basal nuclei, and an understanding of key tracts, pathways and networks will put the radiologist on solid footing to interpret these challenging cases.

Finally, a sound description of the lesion is really important so that, if needed, the radiologist can conduct a thorough search of the literature and compare the case to published examples of similar disease. Sometimes these cases are time-consuming to report due to the time it can take to review the literature and provide an evidence-based interpretation. In some diseases, with limited available publications in the veterinary literature, parallels must be drawn with the human literature.

Consider the distribution of changes: is the lesion focal or multifocal? Symmetric or asymmetric? Does it affect the cerebrum, midbrain, brainstem or cerebellum? Grey or white matter, or both? What is the general brain volume? General loss of brain volume might indicate brain ageing or a neurodegenerative disease. Has additional tissue been added, or is tissue lost or absent? If so, consider the developmental lesions listed below. Are there changes in signal intensity, and specifically where to these occur? Asymmetric focal lesions lacking mass effect may indicate a cerebrovascular accident. Multifocal asymmetric lesions may indicate infectious or inflammatory brain disease. Symmetrical lesions often indicate a metabolic or toxic aetiology, and may represent an inborn error of metabolism and neurodegenerative disease. Pay particular attention to the basal nuclei, white matter tracts and commissures of the brain; this may improve the specificity of the diagnosis, or at least refine the differential diagnoses list. Is there evidence of contrast enhancement, and what is the enhancement pattern?

2. Developmental lesions

A thorough review of intracranial malformations in both dogs and cats is available. (MacKillop 2011)

2.1. affecting the forebrain

Congenital brain malformations are uncommon but not infrequently seen in practices with a moderate neuroimaging caseload. These include:

Cerebrocortical malformations, such as lissencephaly, polymicrogyria, focal cortical dysplasia and heterotypic grey matter; malformations with loss of cerebral tissue include hydranencephaly and porencephaly.

Corpus callosum anomalies, largely hypoplasia or agenesis of various parts of the corpus callosum (and the related holoprosencephaly).

Abnormal fluid accumulations, such as hydrocephalus (which is not uncommon), arachnoid cysts such as quadrigeminal cistern cysts (supracollicular fluid accumulation), meningocele or meningoencephalocoele, epidermoid and dermoid cyst, choroid plexus cyst, ependymal cyst, and adenohypophyseal cyst (Rathke's cleft cyst).

2.2. affecting the cerebellum and caudal fossa

For completeness, caudal occipital malformation syndrome is listed here but as this is not an uncommon condition, further discussion on this will not take place. Other developmental conditions affecting the cerebellum include cerebellar hypoplasia (and cerebellar abiotrophy), and Dandy Walker malformation.

3. Cerebrovascular disease - asymmetric or focal signal alteration

Cerebrovascular disease is not uncommon, and perhaps now is more frequently recognised with the widespread use of diffusion-weighted and susceptibility-weighted imaging (Arnold 2020). The former of these can aid identification of restricted diffusion of water with cytotoxic oedema, and the latter can aid detection of haemorrhage lesions. Cerebrovascular diseases are usually asymmetric and focal lesions, or sometimes multifocal lesions, which can represent cerebrovascular accidents of various ages. Lesions may occur in a recognised vascular territory, affecting larger portions of the cerebrum or cerebellum. Occlusion of smaller perforating arteries can also affect smaller zones, particularly in the mid-brain.

4. Multifocal asymmetric disease

4.1. Infections or inflammatory diseases

It is beyond the scope of this presentation to thoroughly review infectious and inflammatory brain diseases. In brief, common infectious aetiologies include Neosporosis, Toxoplasmosis, Distemper, and Feline Infectious Peritonitis in the cat, bacterial meningoencephalitis, and

brain abscess secondary to penetrating injury or extension of otitis media/interna. Less common agents include amoebic, rickettsial or fungal encephalitis. Much has been published on the meningoencephalitides of unknown aetiology, a group of conditions more common in small breed dogs and encompassing the entities granulomatous meningoencephalitis, necrotising encephalitis, and necrotising leukoencephalomalacia. Although the aetiopathogenesis is not certain, it is presumed to have an immune-mediated aetiology (Barber. 2022).

5. Symmetric lesions

5.1. Age-related brain changes and canine cognitive dysfunction syndrome

Age-related changes to the brain are not rare or unusual, but are included here for completeness. They can produce some changes which might be misinterpreted as neurodegenerative diseases. The main findings include cortical atrophy particularly in the frontal lobe (Tapp 2004), ventricular enlargement, leukoaraiosis (small white matter T2W hyperintensities) (Scarpante 2017), and cerebral microbleeds (Kerwin 2017). Cerebral microbleeds were also associated with renal disease and shorter median survival time, so may not be a 'normal' consequence of ageing.

Findings which have been associated with canine cognitive dysfunction syndrome (canine dementia) include more severe atrophy of the interthalamic adhesion (Hasegawa 2005, Noh 2017), hippocampal atrophy (Dewey 2021).

5.2. Metabolic and neurodegenerative encephalopathies

These encephalopathies may be congenital/hereditary or acquired. Due to the wide-ranging and often overlapping MRI characteristics of metabolic and neurodegenerative diseases, these conditions are often challenging to diagnose. A systematic review and proposed pattern recognition classification of these conditions is available (Miguel-Garcés 2024). This centres on recognising if lesions involve the grey matter, white matter, or both, and on recognising if there is brain atrophy of the forebrain or cerebellum. The list below is adapted from Figure 14 of Miguel-Garcés 2024, a flowchart summarising the group analysis of metabolic encephalopathies.

5.2.1. Causes of alterations in brain volume:

5.2.1.1. Conditions with increased forebrain volume:

Intoxications (except metronidazole), L-2-hydroxyglutaric aciduria, feline hypertensive encephalopathy

5.2.1.2. Conditions with severe forebrain atrophy:

Neuronal ceroid lipofuscinosis

5.2.1.3. Conditions with mild/moderate atrophy OR normal forebrain volume:

Lafora disease, hepatic encephalopathy, gangliosidosis, fucosidosis, thiamine deficiency, canine hypertensive encephalopathy, spongiform encephalopathy, metronidazole intoxication, osmotic demyelination.

5.2.2. Causes of cerebellar atrophy only:

Cerebellar cortical degeneration

5.2.3. Causes of lesions in specific tissue types:

5.2.3.1. Only grey matter:

Thiamine deficiency, metronidazole intoxication

5.2.3.2. Only white matter:

Gangliosidosis, neuronal ceroid lipofuscinosis, fucosidosis, Bomethalin intoxication

5.2.3.3. Both grey and white matter:

5.2.3.3.1.Grey more than white matter:

L-2-hydroxtglutaric aciduria, spongiform encephalopathy in dogs

5.2.3.3.2.Grey and white matter equally affected:

Hepatic encephalopathy, osmotic demyelination syndrome

5.2.3.3.3.White matter more than grey matter:

Hypertensive encephalopathy, intoxication (except metronidazole)

5.2.3.4. Normal brain

Lafora disease, metronidazole intoxication, hepatic encephalopathy

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