

A Practical Approach to White Matter Disease

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Virtually all categories of pathology may cause white matter abnormalities. White matter abnormalities may be seen in congenital, inflammatory, neoplastic, post-traumatic, metabolic, toxic, vascular, degenerative and demyelinating diseases. The primary white matter disorders are classically divided into two groups: dysmyelinating disorders (usually metabolic), in which normal myelin fails to form, and the demyelinating diseases, in which normal myelin has formed and is later destroyed by a myelinoclastic process. The imaging appearance of white matter disease caused by all disease categories is often nonspecific. Nonetheless, it is useful to categorize the white matter diseases based on their appearance on cross-sectional modalities. Thus, in this section, we will consider: 1) multifocal disease, 2) confluent or diffuse disease and 3) selective white matter disease in which there is a geographic predilection for involvement of a specific white matter distribution.

When evaluating a patient with suspected white matter pathology, there are several important imaging considerations. Magnetic resonance (MR) is much more sensitive than computed tomography (CT) for the detection of white matter abnormalities, and is essential to confidently assess for white matter disease. MR is also useful for the evaluation of normal myelination, which appears complete on T1-weighted images between 8 and 12 months and on T2-weighted images between 20 and 24 months of age. When white matter disease is encountered, supplemental pulse sequences are often useful for increasing the specificity of the MR appearance. These include sagittal T2-weighted images to assess for lesions in the corpus callosum of patients with suspected multiple sclerosis. Inversion recovery and magnetization transfer sequences may also increase the specificity of white matter lesions identified on T2-weighted images. In the setting of previous trauma gradient echo imaging to rule out small foci of hemosiderin are useful.

Because the appearance of white matter disease is often nonspecific, supplemental information is crucial when assessing white matter lesions. T1- and T2-prolongation, which generally characterizes white matter pathology, may be due to vasogenic edema, gliosis, demyelination, and inflammatory infiltrates within the brain. Thus, patient demographics, clinical history, laboratory data and physical findings provide

information which helps to limit the differential diagnosis in the setting of white matter disease.

MIMICS OF WHITE MATTER DISEASE

Pathologic processes which may mimic primary white matter disease include neoplasms, which are occasionally diffuse rather than tumefactive. Infiltrating neoplasms such as gliomatosis cerebri may respect the subcortical U-fibers, and thus appear as a primary white matter disorder. With acute hydrocephalus, transependymal CSF, resulting in periventricular interstitial edema, may look similar to small vessel ischemic white matter disease in this distribution. Any process which causes vasogenic edema, gliosis or white matter inflammation may appear similar to white matter pathology.

In addition to other diseases, several normal anatomic MR features may be mistaken for white matter pathology if they are not recognized. For example, perivascular spaces (Virchow-Robin spaces) may mimic focal small vessel ischemic white matter disease. These CSF-filled spaces are actually extensions of the subarachnoid space into the parenchyma surrounding small vessels. Ranging in size from 1-2 mm to greater than 1 cm, perivascular spaces should parallel CSF signal characteristics on all pulse sequences. There is no enhancement associated with perivascular spaces, which are most often visualized in the midbrain, basal ganglia, and subcortical white matter. To rapidly distinguish these from true white matter pathology, examine the first echo of a long TR sequence ("intermediate-weighted" images). The perivascular spaces, which are hypointense on T1-weighted images and hyperintense on T2-weighted images, "disappear" on the intermediate-weighted sequence due to isointensity with adjacent brain parenchyma. On fluid attenuated inversion recovery (FLAIR) images, the Virchow-Robin spaces are predictably very hypointense like the ventricles.

Ependymitis granularis is another normal phenomenon within the brain which may be mistaken for white matter pathology. *Ependymitis granularis* manifests as high signal intensity on long TR images, which caps the frontal horns of the lateral ventricles. This finding may be seen in all age groups and should not be mistaken for periventricular white matter disease.

Finally, dorsal to the lateral ventricles, there may be foci of increased signal on long TR images which persist, in some patients, until the third decade. The high signal is recognized on the intermediate weighted images, but is generally not as bright as CSF on the second echo, or T2-weighted, image. The ill-defined hyperintensities do not directly abut the ventricular margin, as is seen with periventricular leukomalacia. Instead, a border of normal (hypointense) white matter is interposed between the ventricle and the focus of hyperintense white matter on the T2-weighted images. Histologically, they represent areas of incomplete white matter myelination in this characteristic location. These "terminal" myelination zones are most often seen in children, but may be seen in teenagers and young adults as well.

PEDIATRIC WHITE MATTER DISEASE

Although demyelinating disease is most commonly seen in adults, a minority of multiple sclerosis patients are children. Schilder's disease is a primary demyelinating disease of childhood and is considered by some to represent childhood multiple sclerosis. Acute disseminated encephalomyelitis (ADEM) may affect children and adults. This condition is discussed below.

Vascular causes for white matter abnormalities presenting in the pediatric age group usually occur *in utero* or at birth. In premature infants, periventricular leukomalacia (PVL) is the result of ischemic brain injury. In the undeveloped brain, the periventricular white matter represents a "watershed" zone between the ventriculofugal vessels and vessels penetrating from the cortex. Infants under 1500 grams are especially at risk for the development of ischemic injury to this location. The result is loss of white matter, which is most pronounced in the peritrigonal regions, abutting the lateral ventricles. This results in ventriculomegaly, which is characterized by a crenulated appearance of the ventricular margin. The contour of the ventricles in this case is due to the close approximation of the cortical gyri which accompanies loss of the intervening white matter. T2 prolongation (gliosis) of the remaining white matter may border the ventricles.

In the term neonate, the watershed zone is

similar to that in the adult brain. Hypoxic-ischemic injury in this population is thus characterized by parasagittal cortical atrophy. In addition, the basal ganglia and, occasionally, the brain stem and subiculum of the hippocampus may be involved. These areas represent both vascular watershed distributions (cortex) as well as areas of high metabolic demand. Hypotheses regarding the cause of increased sensitivity to hypoxia in these selective regions within the brain include increased metabolic activity due to: 1) active myelination and/or 2) sites of excitatory amino acid receptors. The characteristic appearance in the cortex is a decrease in bulk of the deep gyral tissue, which results in characteristic "mushroom-shaped" gyri, termed *ulegyria*.

There are several metabolic causes of white matter disease which affect the pediatric population. Demyelinating diseases are those disorders in which normal white matter is not formed or maintained. This may be due to disorders in lipid metabolism or other enzymatic deficiencies which include the mucopolysaccharidoses, mitochondrial disorders and the amino acidopathies. These disorders present variably with atrophy, prominent perivascular spaces, and multifocal white matter abnormalities. Distinguishing these disorders on the basis of imaging features alone may be difficult. Evaluation of these patients must include correlation with the age-of-onset, clinical findings, the biochemical profile and information regarding any familial disorders. In some cases, however, there are distinguishing features which facilitate an imaging diagnosis. For example, macrocephaly is a feature of two of the dysmyelinating conditions: Alexander's disease and Canavan's disease. Alexander's disease manifests initially as white matter hypodensity (on CT) and T2 prolongation (on MR) in the frontal white matter, whereas Canavan's disease is generally associated with global white matter involvement, as well as cortical atrophy and ventriculomegaly. A posterior distribution, involving the periatral and occipital lobe white matter, is characteristic of adrenoleukodystrophy (ALD). The corpus callosum and fornix are also typically involved. Both ALD and Alexander's disease may show peripheral enhancement, whereas the other dysmyelinating disorders have not been reported to show significant enhancement. In patients with global dysmyelination, Canavan's disease and Pelizaeus-Merzbacher's disease are considerations. Unlike Pelizaeus-Merzbacher's disease, Canavan's disease spares the internal capsule and, as mentioned above, is associated with macrocephaly. It is

important to bear in mind, however, that all of the dysmyelinating disorders may result in global white matter involvement late in later stages of the disease.

WHITE MATTER DISEASE AFFECTING ALL AGE GROUPS

Adult leukoencephalopathies (and white matter disorders which are not age-specific) may be caused by several categories of disease. Primary demyelinating disorders, infectious, neoplastic, post-traumatic and metabolic disorders are the most common. When white matter disease is encountered on an imaging study, it is useful to first characterize the white matter involvement as multifocal, confluent / diffuse, or selective (geographic). This approach, combined with the clinical information regarding patient demographics, clinical history and physical findings, helps the imager limit the differential diagnosis. As with the pediatric white matter disorders, the multifocal diseases may have a confluent appearance, especially late in the course of the disease. Thus, the categories described below are not mutually exclusive.

MULTIFOCAL WHITE MATTER DISEASE

Multifocal white matter abnormalities are characteristic of multiple sclerosis (MS), a primary demyelinating disease. Multiple sclerosis most commonly affects females, and is most prevalent in the 20-40 year old age group. In middle aged adults, the female-to-male ratio is 1.5-2:1, but in younger patients the female preponderance is greater. Although 75% of patients with multiple sclerosis present between the ages of 20 and 50 years of age, it is important to bear in mind that 15% present in the first and second decade, and 10% present after 50 years of age. A negative brain MR does not exclude multiple sclerosis, as the disease may present with spinal cord involvement only (with a normal cranial MR). In patients with intracranial involvement, the periventricular white matter is most commonly involved, usually with an asymmetrical distribution. Increased specificity is afforded by the presence of lesions in the corpus callosum, cerebellar peduncle, cerebellar white matter, and spinal cord. However, not even lesions in these locations are pathognomonic for multiple sclerosis. A potentially confusing appearance of this disease is produced when lesions appear tumefactive during the acute phase, and demonstrate variable enhancement, ranging from solid to rim-

like. Such lesions have been misdiagnosed as tumor, abscess, and other intracranial masses. With time, the lesions cease to enhance (usually after 1-2 months) and assume a more ovoid or cylindrical configuration. Orientation of these elliptical lesions perpendicular to the long axis of the lateral ventricles is more characteristic of MS. Sagittal T2-weighted or FLAIR images are useful to evaluate for lesions within the corpus callosum, especially at the callososeptal junction. Lesions at this location lend specificity to the imaging appearance. T2-weighted images may also reveal hypointense thalami and putamina bilaterally, which are characteristic of long standing disease. Cerebral atrophy is also characteristic of chronic MS. To further distinguish multiple sclerosis from other white matter lesions, inversion recovery sequences have been recommended, as they may reveal a marked hypointense appearance of MS lesions which is not demonstrated in vascular and other sources for white matter disease.

Acute disseminated encephalomyelitis (ADEM) is essentially a monophasic analog of multiple sclerosis. This post-infectious demyelinating disease is usually seen in younger patients, children and young adults. The autoimmune-mediated white matter inflammation and subsequent demyelination usually presents 1-3 weeks following exposure to a virus or a vaccine. ADEM is steroid-responsive, and usually resolves within 1-2 months, although a minority of patients have permanent sequelae. Occasionally the disease is fatal. On imaging studies, high signal intensity is demonstrated on long TR images within the subcortical and deep white matter. Brain stem, cerebellar and basal ganglia involvement are common. Gray matter involvement is seen more commonly than with multiple sclerosis.

Another cause of multifocal white matter abnormalities results from closed head injury, typically from rapid deceleration with rotation. Diffuse axonal injury results from severe torque/shear forces impacting the brain parenchyma. The interfaces between various brain parenchymal components with disparate densities are the most sensitive to such injuries. Thus, the subcortical white matter at the gray/white matter interface, the corpus callosum and the brain stem are most commonly involved. Regions of T1- and T2-prolongation are seen in the acute phase of the disease. Chronically, focal hemosiderin deposition may be present as the only evidence of injury in the wake of diffuse axonal injury. These chronic residua of closed head injury are best detected using gradient-echo MR sequences.

Perhaps the most commonly encountered form of white matter disease in adults is due to small vessel ischemic disease. Although diabetes mellitus, hypertension, and other risk factors may predispose patients to an earlier onset and more severe involvement, there is significant overlap in the degree of parenchymal small vessel change in otherwise healthy patients and those with the aforementioned underlying disorders. And except in very severe cases, the degree of white matter involvement does not predict brain function. The sites most commonly involved include the periventricular and subcortical white matter, the pons and basal ganglia. Cavitary changes may be a feature of small vessel ischemia, and result in signal characteristics which parallel CSF on all pulse sequences. In contrast to demyelinating disease, the corpus callosum and posterior fossa are usually spared by small vessel ischemic disease. With more severe involvement, the white matter hyperintensities coalesce and the process appears diffuse, rather than multifocal.

Vasculitis is another vascular cause for multifocal disease, which may mimic multiple sclerosis in terms of imaging appearance and patient demographics. CNS vasculitis may be seen with systemic lupus erythematosus, Sjogren's syndrome, Behcet's disease and polyarteritis nodosa. Hyperintense foci on long-TR images are characteristic. The T1- and T2-prolongation may reverse. Hemorrhage is not uncommon in these patients, but it would be an unusual feature of either small vessel ischemic disease or multiple sclerosis.

Progressive multifocal leukoencephalopathy (PML) is essentially restricted to the immunocompromised patient population, with a male predominance. This disease results from reactivation of a papova virus, the so-called JC virus. Although this entity was originally described as a multifocal process, it may present with confluent or diffuse regions of white matter involvement. The subcortical white matter and the corpus callosum are most commonly involved, although gray matter may be involved in up to 50% of these patients. The predilection for the subcortical white matter may help distinguish it from HIV encephalitis, which favors the periventricular white matter. With corpus callosum involvement, this process usually crosses the midline. Enhancement, mass effect and hemorrhage are uncommon, but reported, features of PML.

Early metastatic disease may have an appearance similar to multifocal small vessel ischemic changes in the white matter (multiple punctate foci of T1- and T2-prolongation involving white matter). Gadolinium-enhanced images are useful for

distinguishing these disorders, as metastatic disease to the central nervous system virtually always enhances.

Multifocal white matter changes may be also be seen with inflammatory disorders such as Lyme disease and neurosarcoidosis. Associated features with these inflammatory conditions may include enhancement of the cranial nerves or basilar meninges.

DIFFUSE/CONFLUENT WHITE MATTER DISEASE

Diffuse or confluent white matter disease may be seen in the later stages of any of the above multifocal processes. Also, vasogenic edema may appear as a confluent region of T1- and T2-prolongation confined to the white matter. An underlying mass should distinguish vasogenic edema surrounding a neoplasm or infection from a primary white matter process. As mentioned above, infiltrating neoplasms may make this distinction difficult.

Radiation changes may induce diffuse white matter hyperintensity on long TR MR images. The clinical history usually explains this finding. Acutely, edema is present within the white matter. Small vessel damage resulting in eventual vascular lumen compromise results in demyelination and atrophy. More localized disease may be demonstrated if a limited radiation port was employed.

In patients who have received high dose radiation therapy for intracranial neoplasms, it may be difficult to distinguish a neoplasm from radiation necrosis, which often demonstrates mass effect, and variable enhancement in the setting of T1- and T2-prolongation. Serial exams in this case will reveal involution, rather than expansion, of the lesion. Positron emission tomography imaging is occasionally useful to distinguish these entities, as radiation necrosis is hypometabolic, as opposed to neoplasms. Perfusion MR imaging may also prove useful for distinguishing recurrent tumor from radiation necrosis.

Another complication of tumor therapy is diffuse necrotizing leukoencephalopathy (DNL), which causes diffuse white matter injury following chemotherapy, with or without concomitant radiation therapy. DNL likely results from synergistic deleterious effects of radiation therapy and chemotherapy (methotrexate is a common offender). This disorder has a rapid clinical course usually leading to death. The confluent regions of T1- and T2-prolongation are characterized by variable peripheral enhancement on post-gadolinium studies. The centrum semiovale is characteristically involved.

In children, a late sequela of radiation injury may include mineralizing microangiopathy. This disorder may also result from combined radiation and chemotherapy. It produces diffuse low attenuation (on CT) and T1- and T2-prolongation (on MR) in the white matter. Focal calcifications are characteristically present in the basal ganglia and at the gray/white matter interface in this disorder. Cortical atrophy is another feature evident on imaging studies.

Sporadic viral encephalitis will occasionally present with diffuse white matter abnormality. This appearance is nonspecific, as opposed to the distinctive geographic predilection for the medial temporal lobes seen with herpes encephalitis. In AIDS patients, HIV encephalitis is present in majority of cases. It manifests clinically with progressive dementia. On MR studies, ill-defined and symmetric white matter hyperintensities with no associated enhancement or mass effect. Cytomegalovirus commonly infects the brain in this population. The periventricular white matter is typically involved and, unlike HIV encephalitis, enhancement is usually demonstrated on post-contrast images.

GEOGRAPHIC WHITE MATTER DISEASE

Some white matter disorders are geographically selective, and thus manifest with characteristic MR imaging appearances which convey the diagnosis. Central pontine myelinolysis, or osmotic demyelination syndrome, is a striking example. This disorder, which is likely due to a rapid or over correction of hyponatremia, is often seen in chronic alcoholics, and in victims of malnutrition or chronic debilitating disease. The corticospinal tracts and peripheral pons are characteristically spared early in the course of the disease, and a characteristic "bat wing" configuration is localized to the central pons. There may be extension to the midbrain and basal ganglia (so-called *extra pontine myelinolysis*). The disease manifests with low density on CT images, and T1- and T2-prolongation on MR.

Another white matter disorder with a characteristic distribution is Marchiafava-Bignami disease. This entity was originally described in Italians with excessive (low-quality) red wine intake. The disease has since been described in other populations and in association with other products of the vine. In patients with Marchiafava-Bignami disease, demyelination and necrosis characteristically involved the corpus callosum and adjacent white matter. It manifests as low density in the corpus callosum on CT. With MR, the corpus

callosum and deep white matter show high signal on long-TR image.

The rare hereditary sensorimotor neuropathy which affects some native Americans, Navajo neuropathy (type A), can be distinguished from the leukodystrophies clinically. On cranial imaging, characteristic lesions in the cerebellar white matter may be identified. They are crescentic in configuration, low attenuation on CT, and show T1- and T2-prolongation on MR.

More of a physiological phenomenon than a disease, Wallerian degeneration usually involves the corticospinal tracts. Injury to nerve axons anywhere along their course results in axonal involution and demyelination. In the chronic phase, a focus of T1 and T2 prolongation with accompanying atrophy may be seen along the course of the involved white matter tract. The cerebral peduncles are characteristically involved.

SUMMARY

Although the imaging appearance of white matter pathology may be nonspecific, the diagnosis of white matter disease may be managed through the judicious use of magnetic resonance imaging. In combination with knowledge of the imaging manifestations of white matter diseases and the patient's clinical history, laboratory data and physical exam findings MR facilitates the generation of a limited and accurate differential diagnosis.

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