Pictorial Essay
‘White Dots’ on Cranial MRI: MS and Differential Diagnosis

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Introduction
Demyelinating disorders of the central nervous system (CNS) have a variety of aetiologies and can be separated into primary (e.g., multiple sclerosis) and secondary (e.g., infectious, ischemic, metabolic or toxic) diseases. Providing high spatial and contrast resolution, cranial MRI is the imaging modality of choice to assess demyelinating disorders [1].

Multiple sclerosis is the most common primary demyelinating disease of the CNS. However, differentiation from other demyelinating disorders might be challenging since clinical findings can be subtle and imaging is not always specific [2, 3]. Hence, precise assessment of lesion localization and morphology (over time) as well as clinical and laboratory results are essential for the correct diagnosis [1].

This pictorial essay is intended as an overview of the spectrum of demyelinating disorders and their typical and atypical imaging findings.

Multiple Sclerosis (MS)
MS is a chronic, immune-mediated demyelinating degenerative disease of the CNS and the leading cause of non-traumatic neurological disability in young and middle aged adults. Dissemination of disease in space and time proved by either clinical, paraclinical or laboratory assessments is an essential diagnostic criterion for MS [1, 4]. Differential diagnosis for the clinical presentation must be considered and excluded before MS can be diagnosed [2, 5]. Cranial MRI shows lesions in at least 95% of MS patients and plays a key role in diagnosis and follow-up. The 2010 revision of the McDonald Criteria defining dissemination in time (DIT) and space (DIS) has simplified the diagnostic criteria of MS and resulted in earlier and more reliable diagnosis [6]. As a consequence, therapy can be started earlier resulting in patients’ improved quality of life.

McDonald criteria 2010
DIS:
≥ 1 T2 lesion in at least 2 of 4 areas of the CNS
• Periventricular
• Juxtacortical
• Posterior fossa
• Spinal cord

DIT:
1. A new T2 and/or gadolinium-enhancing lesion on follow-up MRI, with reference to a baseline scan, irrespective of the timing of the baseline MRI.
2. Simultaneous presence of asymptomatic gadolinium enhancing and non-enhancing lesions at any time.

Typical imaging findings of MS
The demyelinating lesions in MS are typically multiple, well-defined and ovoid, preferentially involving the corpus callosum (up to 93%), periventricular white matter, subcortical regions (including U-fibres), optic nerves (50%) and visual pathways, the posterior fossa (68% brain stem, up to 49% cerebellar lesions) and cervical spinal cord (56%) [1, 7, 8] (Fig. 1).

Typical signs of MS are (Fig. 2):
• ’Finger prints’: Typical morphology of lesions of the corpus callosum in MS patients at the undersurface of the corpus callosum.
• ’Dawson’s fingers’: Ovoid lesions radially oriented perpendicular to the lateral ventricles, which represent the perivascular pattern of inflammation along the medullary veins.
• ’Open ring’ sign: Lesions with an open ring enhancement, which are highly specific for demyelinating processes and may help in differentiating atypical demyelination from neoplasm or abscess.

Continued on page 35.
Typical locations of MS plaques.

(1A) Involvement of the corpus callosum; (1B) Lesions at the callososseptal interface; (1C) Ovoid, well-defined lesions in the periventricular and (1D) subcortical white matter; (1E) Affection of the optic nerve; (1F) Lesion in the brain stem; (1G) Small plaques in the cervical spinal cord.
Typical imaging signs of MS.
(2A) Finger prints at the undersurface of the corpus callosum; (2B) Dawson-fingers reflecting the perivenular inflammation; (2C) Open ring sign of enhancing lesions.

Assessment of lesion load in the posterior fossa.
(3A) FLAIR versus (3B) T2-weighted images.
Imaging appearance

MS plaques show high signal intensity on T2w and low signal intensity on T1w reflecting the loss of myelin and increase in water content. FLAIR is the preferred sequence for assessing lesions of the corpus callosum, often the first area involved. Suppression of the cerebrospinal fluid (CSF) signal makes periventricular lesions at the callososeptal interface more conspicuous [1]. For the assessment of lesions in the posterior fossa, however, T2w is superior to FLAIR [7] (Fig. 3). Active plaques with high cellular lymphocytic infiltrate may show reduced diffusivity in diffusion-weighted imaging (DWI) with corresponding low signal on apparent diffusion coefficient (ADC) maps [1]. Inactive lesions are hypocellular with increased ADC. Acute lesions may also show a halo of less striking hyperintensity, presumably as a result of transient edema [8] (Fig. 4). 5–10% of lesions also involve grey matter and are difficult to detect with conventional MRI [8]. Double inversion recovery sequences might be helpful to better assess cortical lesions. Some T1w hypointensities disappear as the edema resolves and remyelination occurs, while some remain and develop into ‘black holes’, reflecting more aggressive tissue destruction and axonal loss (Fig. 5). Active lesions may show contrast enhancement due to inflammation-related blood-brain barrier breakdown [1]. Enhancement patterns may be solid, ring or arc like and persist for 4–6 weeks. Open ring enhancement is highly specific for demyelinating lesions [9]. Corticosteroids obtrude the blood-brain barrier so that enhancement stops 48 hours after therapy starts. Similar to brain metastases, the use of double dose contrast media and an increased time delay between contrast application and scanning both improve the detection rate of enhancing lesions. Spinal cord plaques occur in 83% of MS patients and can help to narrow differential diagnosis where there is uncertainty. The preferential location is the peripheral cervical and also thoracic cord. Acute plaques cause cord swelling and may show contrast enhancement. Cord atrophy may be seen in advanced MS, probably reflecting axonal loss.

Red flags

Red flags are clinical, laboratory or imaging findings that should alert clinicians to consider alternative diagnoses [10].

Major imaging red flags include:

- Cortical infarctions (consider embolic disease, vasculitis)
- Lacunar infarctions (consider hypertensive ischemic disease, CADASIL, Susac’s syndrome)
- Haemorrhages/microhaemorrhages (consider amyloid angiopathy, CADASIL, vasculitis)
- Mainly (sub)cortical location (consider age-related change, small vessel disease, vasculitis, progressive multifocal leukoencephalopathy)
- Symmetrical lesions (consider leukodystrophy)
- T2 hyperintensities of the temporal pole and external capsule/insula (consider CADASIL)
- Large lesions (consider glioblastoma, lymphoma, progressive multifocal leukencephalopathy)
- Central brainstem lesions (consider central pontine myelinolysis, hypoxic-ischemic conditions, infarct)
- Meningeal enhancement (consider chronic meningitis, sarcoidosis, CNS vasculitis)
- Persistent gadolinium enhancement (> 6 weeks) and continued lesion enlargement (consider lymphoma, glioma, vasculitis, sarcoidosis)
- Complete ring enhancement (consider brain abscess, glioblastoma, brain metastasis)
- Simultaneous enhancement of all lesions (consider acute disseminated encephalomyelitis (ADEM), vasculitis, lymphoma, sarcoidosis)
Tumefactive demyelinating lesions (TDLs)

TDLs are solitary lesions, which may simulate neoplasms or abscesses. Clues to the diagnosis include less mass effect than expected for their size, an arc-like incomplete ring enhancement, no increased perfusion and visualisation of veins coursing through the lesion – all untypical of tumor or abscess [9, 11]. On the contrary, abscesses and highly cellular tumors like CNS lymphomas show restricted diffusivity with low ADC values.

37-year-old woman presenting with a progressive left-side hemiparesis.
(6A) Large hyperintense lesion in the deep white matter of the right precentral area with only a little mass effect and (6B) ring enhancement.

Active lesion in the right periventricular white matter with (4A) decreased diffusivity on ADC map and (4B) a halo of less striking hyperintensity on axial FLAIR.

'Black holes' as a sign of advanced tissue destruction. (5A) 'Black hole' in the white matter of the right frontal lobe (5B) 'Black holes' at the occipital horns of the lateral ventricles.
Radiologically isolated syndrome (RIS)

This syndrome refers to incidentally identified cerebral lesions on MRI meeting the characteristic imaging criteria of MS in subjects without any clinical symptoms. Up to half of the patients, however, develop neurological symptoms on follow-up, around two-thirds show radiological progression within 5 years. Clinical conversion is more likely in patients with a high number of MRI lesions (> 9), gadolinium enhancing lesions, and especially the presence of asymptomatic cervical cord lesions. Some clinicians advocate a ‘wait and see’ strategy, while others propose MRI and clinical follow-up examinations. However, treatment with disease-modifying drugs is not advisable at this stage [12, 13].

Neuromyelitis optica (NMO)

NMO or Devic disease is an autoimmune, inflammatory demyelinating disorder of the CNS with predominant affection of the optic nerve (optic neuritis) and spinal cord [14, 15]. Cord lesions on MRI are usually extensive (involving at least 3 vertebral segments) and centrally located, with or without enhancement. Optic nerve lesions may be uni- or bilateral with high T2 signal of the swollen optic nerve segment [16]. Although brain lesions do not normally show the MS-typical configuration, lesions are indistinguishable from MS in 10% of cases [17].

MRI findings in a middle-aged woman with anti-AQP-4 antibodies, lymphocytosis in the cerebrospinal fluid and symptoms of optic neuritis and acute myelitis. (8A) T2w sagittal with an extensive, centrally located area of high T2 signal within the cervical cord associated with cord swelling. (8B) High T2 signal of the right optic nerve in the intracranial part (8C) with corresponding contrast enhancement on T1w imaging.

31-year-old man with incidentally recognized MS-like lesions on cranial MRI. He had no clinical history and there were no abnormal findings on examination. (7A) Small, ovoid hyperintensities especially in the periventricular white matter (7B) Radially oriented lesions perpendicular to the lateral ventricles on sagittal FLAIR.

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Acute disseminated encephalomyelitis (ADEM)

Caused by an allergic or autoimmune cross-reaction with viral protein, this inflammatory, mostly monophasic demyelinating disease of the CNS usually appears days to several weeks after viral infection or immunisation with clinical symptoms of severe encephalopathy, fever, variable focal deficits and drowsiness. ADEM causes a diffuse perivenous inflammatory process with multiple poorly marginated confluent lesions, typically larger and without dissemination in time than those of MS (often > 1.5-2 cm) [16]. The subcortical and deep white matter is more often affected than periventricular regions, lesions are not oriented perpendicular to the lateral ventricles, and one third of cases show additional cord lesions [14]. The lesions usually resolve completely in up to 75% of the cases.

Acute demyelinating encephalomyelitis (ADEM) in a young woman. MR images show multiple, supra- and infratentorial, bilateral, poorly defined, large T2 hyperintense (9A, B), T1 hypointense (9C, D) and contrast enhancing (9E, F) lesions. Few weeks before, the patient had a pulmonary infection.
Neuroborreliosis
(Lyme disease)

Lyme disease is a multisystem inflammatory disorder caused by an infection with Borrelia burgdorferi. Patients usually present with severe headache and influenza-like illness. MRI shows hyperintense small periventricular white matter lesions (resulting from demyelination), which can mimic MS. Lesions may enhance or show decreased diffusivity. Also enhancement of the facial nerve, cauda equina and meninges can be found [14].

In addition, there are some other rare infections that might resemble MS, such as Whipple’s disease, neurosyphilis, HIV encephalitis, Creutzfeldt-Jakob disease, brucellosis or HHV-6 infection [18].
Neurosarcoidosis

Sarcoidosis is a multisystem granulomatous disease of unknown aetiology most frequently affecting the lungs. In 3-5% of patients with sarcoidosis the CNS is involved. Optic neuritis, acute transverse myelitis or brainstem syndromes may be present. Basal meningitis, hypothalamic involvement, hydrocephalus and manifestations around the pituitary fossa, however, are more common signs of Neurosarcoidosis, which help to differentiate between neurosarcoidosis and MS [14].

Susac’s Syndrome

Susac’s syndrome is characterized by the clinical triad of multifocal encephalopathy, branch retinal artery occlusion and hearing loss. Histopathologically, Susac’s syndrome is based on a microangiopathy of the brain, retina and cochlea, suggested to be caused by an immune-mediated damage of the endothelial cells. MRI shows multiple small white matter lesions (corresponding to microinfarctions) preferentially involving the centre of the corpus callosum. These ‘snowball’ lesions are pathognomonic for Susac’s syndrome. Microinfarctions may also extensively involve the internal capsule, basal ganglia and thalami in 70% of cases and additional leptomeningeal enhancement is seen in about 30% of cases [19].
Cerebral autosomal-dominant arteriopathy with subcortical infarctions (CADASIL)

CADASIL is a hereditary small-vessel disease of the brain associated with a mutation of a NOTCH 3 gene. Patients develop recurrent stroke-like episodes, migraine-like headaches and subcortical dementia [20]. Cranial MRI shows diffuse ischemic-derived T2 hyperintensities in deep white matter. Involvement of the anterior temporal lobes and external capsule are pathognomonic for CADASIL [21]. Common changes also include lacunar infarctions in the pons, internal capsule, thalami and basal ganglia, involvement of the U-fibres and multiple scattered microhaemorrhages. The corpus callosum and posterior fossa are rarely affected.

Subcortical arteriosclerotic encephalopathy (SAE, Binswanger’s disease)

Caused by ischemia of the deep central white matter, Binswanger’s disease presents with extensive white matter changes that spare the periventricular region and extend into the corona radiata [14]. The age of the patients at clinical onset, sparing of U-fibres and missing involvement of the corpus callosum help to differentiate it from MS [16].
Leukodystrophies
These are hereditary metabolic disorders with progressive white matter lesions, which tend to be bilateral and symmetrical with an antero-posterior gradient of progression [21]. With the exception of adrenoleucodystrophy, these disorders do not show contrast enhancement.

Mitochondrial diseases
This is a group of rare multisystem disorders caused by a variety of genetic defects affecting the mitochondrial metabolism. Especially Leber’s hereditary optic neuropathy, chronic progressive ophthalmoplegia and mitochondrial encephalomyelopathy, lactic acidosis and stroke-like episodes (MELAS) might be difficult to distinguish radiologically from MS. Multisystem involvement, clinical presentation including a positive family history as well as calcified cerebral lesions might be the clue to the correct diagnosis [5].

*Siemens disclaimer: MR scanning has not been established as safe for imaging fetuses and infants less than two years of age. The responsible physician must evaluate the benefits of the MR examination compared to those of other imaging procedures.

Follow-up MRI examinations in a child* with a mitochondrial disease and lactic acidosis. (16A, B) Examination at the age of 8 years old* with large, asymmetrical and multiple areas of high T2 signal in the deep periventricular and subcortical white matter and in the basal ganglia (a) with haemorrhages within the basal ganglia on native T1w (b). (16C, D) Follow-up examination at the age of 12 years old* after drastic progression with vast white matter changes, affection of the cerebral peduncles and mesencephalon and progressive atrophy with enlargement of the ventricles.
Vasculitis

Several vasculitic disorders may involve the brain, like systemic lupus erythematosus (SLE), Wegener’s granulomatosis, Behçet’s syndrome, polyarteritis nodosa or Sjögren’s syndrome. Patients may present with cortico-subcortical or MS-like periventricular lesions on MRI. Isolated angiitis of the CNS is a rare disorder with granulomatous inflammation of small cerebral parenchymal or leptomeningeal vessels. Patients present with severe headache and focal neurological signs. MRI may show focal lesions similar to MS, diffuse white matter changes, involvement of grey matter structures, infarctions, haemorrhages and leptomeningeal or parenchymal enhancement [5]. High-resolution time-of-flight MR angiography is a reasonable initial modality in the investigation of suspected CNS vasculitis (demonstrating multiple stenosis also affecting peripheral arteries), but in case of normal MRA, catheter cerebral angiography should be considered.

Cerebral vasculitis. FLAIR (17A) and contrast-enhanced T1w axial (17B) MR images show multiple contrast-enhancing foci of high T2 signal in the periventricular and subcortical white matter, similar to MS. (17C) TOF-MR angiography shows multifocal, segmental narrowing of the intracranial vessels mainly in the anterior circulation. (17D) Catheter cerebral angiography proves the finding of vasculitis.
Normal aging phenomena

Multifocal areas of T2 hyperintensity in the periventricular or deep white matter have been reported in around 35% of healthy individuals over the age of 60 years. Lesions may be small, multiple and punctuate or large and confluent. These non-specific, age-related, asymptomatic foci of ischemic demyelination may lead to misdiagnosis or underdiagnosis of MS especially in patients over 50 years old [14].

64-year-old healthy male with age-related, partially confluent periventricular foci of high T2 signal on axial FLAIR.

Conclusion

There is a variety of aetiologies for demyelinating processes of the CNS. MRI is the preferred imaging technique for diagnostic workup. Knowledge of the typical and rather unusual MR features of MS as well as consideration of the patient's age, clinical history and laboratory evaluation is essential to narrow the differential diagnosis.

References


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