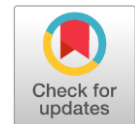


## Role of Clinicoradiological Correlation in Evaluation of Various Demyelinating Disorders: A Systematic Review

**Rohail Razzaq<sup>1,2</sup>, Muhammad Hamza Khan<sup>3</sup>, Hafiza Fajar Shabbir<sup>4</sup>, Nimra Tauseef<sup>5</sup>, Sadiqa Arshad<sup>6</sup>, Muzammil Rasheed Bhutta<sup>7</sup>**

1. Radiology, Mufti Mehmood Teaching Hospital, Dera Ismail Khan, Pakistan
2. Royal Derby Hospital, Derby, GBR, United Kingdom.
3. Emergency Medicine/Physiology Department, Abbottabad International Medical Institute, Abbottabad, Pakistan.
4. Pathology Department, Lahore Medical and Dental College, Lahore, Pakistan.
5. Internal Medicine Department, Fauji foundation Hospital Rawalpindi, Rawalpindi, Pakistan.
6. Psychiatry Department, Mukhtar A. Sheikh Memorial Welfare Hospital (MASH), Multan, Pakistan.
7. Radiology Department, Shaukat Khanum Memorial Cancer Hospital Lahore, Pakistan



\*Corresponding Author: Rohail Razzaq, Email: [razzaqrohail8@gmail.com](mailto:razzaqrohail8@gmail.com), Cell: +923499008655

### ABSTRACT

**Background:** There are mainly three types of white matter disorders resulting from defective myelination (dysmyelinating), destruction of myelin (demyelination) and decreased myelination (hypomyelinating). Each of these disorders require MRI and specific imaging for diagnosis. However, diagnosis of white matter disorders cannot solely rely on imaging.

**Objective:** In this review we aim to correlate clinical presentation, history, laboratory investigations, and imaging as a tool rather than diagnostic modality to highlight the importance of clinical and radiological collaboration to diagnose the exact disease process. We would specifically discuss variants of multiple sclerosis, acute disseminated encephalomyelitis, neuromyelitis Optica spectrum disorder, progressive multifocal leukoencephalopathy, and osmotic demyelination syndrome. This study also includes specific signs of different demyelination white matter disorders on MRI which are characteristic of that disease process. However, we also highlight what clinical correlation and investigations may further aid to confirm the diagnosis, prognosis and extent of disease progression.

**Methods:** In this review article we used Prisma guidelines where there was evidence of better patient outcome in terms of clinicoradiological collaboration in diagnosing various demyelinating white matter disorders.

**Results:** We found that timely diagnosis and better patient outcomes can be achieved if clinicians also take in accord their own clinical judgement and based on that order relevant radiological investigations resulting better clinician to clinician communication, judicious use of hospital resources and overall better outcome in disease process.

**Conclusion:** Our study concludes that solid clinical judgement, laboratory investigations along with radiological features of disease process would enhance clinical outcomes in terms of timely diagnosis, specific treatment and tracking disease prognosis.

**Keywords:** Multiple Sclerosis, Neuromyelitis Optica spectrum disorder, Acute disseminated encephalomyelitis, MRI, Diffusion weighted imaging, Contrast enhanced, Progressive multifocal leukoencephalopathy, Osmotic demyelination syndrome, T2 weighted imaging, T1 weighted imaging.



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## INTRODUCTION

Magnetic resonance imaging (MRI) in the past decade has become first go investigation for any suspected demyelinating white matter disorders. White matter diseases encompass abnormal myelination (dysmyelination disorders) [1]. Demyelinating disorders can be due to number of aetiologies including inflammation, infection, ischemia or toxins resulting in destruction and damage of white matter. MRI features have become major diagnostic criteria for many demyelinating disorders, namely multiple sclerosis (MS), Neuromyelitis Optica spectrum disorder (NMOSD), and acute disseminated encephalomyelitis (ADEM) [2]. Similarly, white matter disorders can be caused by abnormal myelin breakdown (demyelinating disorders) and deficiency in normal myelin development (hypomyelination disorders) [3]. MRI is preferred imaging for diagnosis and evaluation of disease progression due to its high-resolution images without radiation exposure and being non-invasive. Moreover, with advent of multiple pulse sequences that provide wide array of information about structure and even function of area of interest which allows investigation of different pathological tissue properties [4,5]. However, recent analyses of clinical trial data show a mismatch of disease severity on MRI and clinical course also known as clinic radiological paradox [6]. We would specifically discuss variants of multiple sclerosis, acute disseminated encephalomyelitis, neuromyelitis Optica spectrum disorder, progressive multifocal leukoencephalopathy, and osmotic demyelination syndrome. This review examines how neuroimaging techniques help in diagnosis, prognosis, track disease progression, and aid research in different white matter disorders, yet sometimes radiological features may overlap which requires acquiring specific imaging techniques along with clinical correlation. This study also includes specific signs of different demyelination white matter disorders on MRI which are characteristic of that disease process. However, we also highlight what clinical correlation and investigations may further aid to confirm the diagnosis, prognosis and extent of disease progression. Clinical presentation and specific history taking is also central to reach a working diagnosis followed by judicious use of relevant imaging. Additionally, a specific study that compares different clinical presentations and radiological features has not been conducted in terms of demyelinating white matter disorders. This article aims towards better collaboration and communication between clinicians and radiologists which can result into improved patient outcomes. In our study we aim to explore MRI sequences and diagnostic features of different white matter disorders along with clinical features and pertinent investigation that are essential to confirm the radiologic findings. Subsequently, we review various demyelinating disease features on MRI.

## MATERIALS AND METHODS

The inclusion and exclusion criteria (Table 1) were used to identify the studies on demyelinating disorders including RRMS, RIS, CCM, TMS, MMS, BCS, NMSOD, ADEM, PML, and OS. Rapidly progressive demyelinating disorders such as leukodystrophy were also excluded. The interventions (Table 2) were clinical correlation with MRI and other imaging studies including the McDonald criteria for the diagnosis of multiple sclerosis and histopathological correlation to distinguish other conditions such as tumefactive demyelination. The following types of investigations were excluded: studies based solely on imaging. The intervention and comparison (Table 3) involved using clinical presentations and histopathological correlation with imaging in the diagnosis of diseases as opposed to solely using imaging. The selection criteria which incorporate both McDonald criteria were used as the benchmark. The expected outcomes (Table 4) were designed to result in timely and accurate diagnoses and early treatment where applicable especially for MS so as to enhance the patients' well-being. The tasks included in the research plan (Table 5) included conducting the search of systematic reviews, selecting the studies and writing the discussion and conclusion sections. The relevant data for the review were obtained from the databases such as PubMed, Radiopedia, and Google Scholar.

**Search Plan:** The items that were included in the search string are: search filters and mesh or other terms. The search string and items were created by health librarian. The author [NT] and health librarian helped in the designing the search plan and followed by peer review in accordance with PRESS guidelines. Authors (RR, HM) designed and ran the search plan.

No restrictions in terms of publication type were applied. Studies that were in English language or had been translated to English were included. Authors (RR, HM, NT) removed the plagiarism in the results. Subsequently, reference lists of all included studies were also evaluated and used the similar article features. Authors (FS, HM) conducted the supplementary searches.

**Search sources:** Databases used for the search were PubMed, The Cochrane Library for Cochrane Reviews, Scopus, Radiopedia and Google scholars from inception until 7th July 2024 (see References).

PubMed - run 7/7/2024

The Cochrane Library for Cochrane Reviews - run 7/7/2024

Scopus - run 7/7/2024

Radiopedia - run 7/7/2024

Google scholars - run 7/7/2024

**Article selection and screening:** Results from search were screened by authors (RR, HM) independently for eligibility in this review. Discrepancies arising during study process were resolved by consulting third author or

consensus and full texts from each of the included studies were reviewed by authors (RR, HM, SN) to determine if they should be included. Authors (SN) screened trials. Only studies relevant to inclusion criteria of research question were included (table.1). The studies which showed clinoradiological correlation of disease process were included.

**Publication Bias:** We assessed publication bias / small studies effect using Funnel plot.

**Demyelinating disorders:** Multiple sclerosis (MS) is a common demyelinating white matter disease involving central nervous system characteristically number of lesions affecting in different areas of CNS (space) and occurring at different times (in time) [4,7]. Multiple sclerosis has multiple variants characterized by their own typical imaging features and clinical presentation. These include classic multiple sclerosis (Charcot type), tumefactive multiple sclerosis, Marburg type (acute malignant), and bale concentric sclerosis This article discusses most of the multiple sclerosis variants under separate headings.

**Classic multiple sclerosis (Charcot type):** The diagnosis of MS is multi-pronged attempt including MRI imaging with different sequence acquisition, objective clinical evidence, and CSF-specific oligoclonal bands in terms of laboratory investigations.

**MRI features:** T2 weighted imaging the sequences which are classic to detect MS lesions are T2 weighted imaging (T2WI) which are known to be hyperintense (Figure 1). However, limitation to T2WI is that clear distinction of demyelination from other pathologic processes that are associated with demyelination (e.g. remyelination, inflammation, edema, Wallerian degeneration, neoplasm, infection, etc.) is difficult as they may have similar hyperintense T2WI [5,8]. Specific criteria (McDonald criteria for diagnosis of multiple sclerosis) using all above investigations/clinical evidence is used to pinpoint the diagnosis, indicating that MRI is just a facet to diagnose and monitor the disease progression [9]. Fast spin echo (FSE)-based techniques and fluid attenuation inversion recovery (FLAIR) is answer to above mentioned limitation as this sequence uses and additional recovery pulse to suppress cerebrospinal fluid (CSF) signals. FLAIR Improved contrast of FLAIR images make the hyperintense lesion easier to spot. An early imaging feature detectable is ependymal dot-dash sign which are seen as high signals along corpus callosum which often propagate to lateral ventricles in triangular fashion best seen on parasagittal images which are most frequently seen lesions located perpendicular to axis of lateral ventricles termed as Dawson's fingers [10] (Figure 1,2). FLAIR has limitations as well due it's relatively reduced sensitivity to show lesions in posterior fossa [11]. However, T2WI has been found to be superior in detecting posterior fossa lesions (Figure 3).

T1 weighted imaging mostly shows iso to hypointense lesions namely T1 black holes are usually

detectable in an early stage which is transient [12]. And when these lesions are found across callososeptal interface are termed as Venus's necklace, but in advanced disease with accompanying brain atrophy hyperintense lesions can be found. T1 black holes in 30 % of the case can be persistent and the characteristic of chronic T1 black hole lesions is severely decreased N-acetylaspartate (NAA) on MR spectroscopy. Chronicity of T1 black holes' better correlates with disability compared to T2 lesion load [12]. T1 contrast enhanced (gadolinium) is known to be characteristic for lesions with active disease process which show post contrast enhancement which is incomplete along the edges rendering the appearance of an open ring enhancement showed in (Figure 04). Gadolinium enhancement is typically noticed around 4-6 weeks of lesion formation marking recent or ongoing disease activity [13].

Double inversion recovery (DIR) acquisition technique has an improved sensitivity to pin point cortical lesions in comparison to FLAIR and T2WI sequences. T2WI sequences have limitations in detection of cortical grey matter lesions and along with subsequent advanced cortical atrophy these changes correlate more with clinical outcomes showed in (figure 05) [14].

Now as discussed above MRI provides a wide range of information about the disease process, yet each sequence has its own limitation and further clinical correlation is deemed central to diagnose and monitor disease progression. T2WI sequences are crucial, yet a paradox exists lesion load often weakly correlates with a patient's disability. This clinoradiological paradox is particularly evident in relapsing-remitting MS (RRMS) particularly during later stages, which can be partly due to remyelination as these areas may mimic active lesions on T2WI, lesion merging lesions can underestimate overall burden on MRI and brain atrophy with disease progression can often create the illusion of decreasing lesion load [15]. Ring-enhancing lesions can appear uniform, patchy (nodular), or with a specific open ring pattern, while contrast enhanced lesions can occur in demyelinating diseases like MS, many other conditions can also cause them, including gliomas, metastasis, infections, and abscesses [16,17, 18]. However, there are features for MS contrast-enhanced lesions that can differentiate them from others such as shorter duration contrast enhancement, low signal intensity on apparent diffusion coefficient (ADC) and magnetization transfer ratio (MTR) [19]. Given the above limitations, it is necessary to correlate with disease progression, McDonald's criteria and utilize each sequence to supplement the clinical information for diagnosis.

**Radiologically isolated syndrome:** Radiologically Isolated Syndrome (RIS) is characterized by MRI features in accordance with McDonald's criteria for multiple sclerosis yet patient is clinically asymptomatic [20]. The lesions often meets the McDonald's criteria of distribution in space with or without dissemination in time, but when

neurological symptoms develop its termed as conversion which can be predicted by imaging features including lesions with post contrast enhancement, hyperintense T2 lesion load, presence of lesions in infratentorial location as well as spinal cord lesions which are deemed to be one of the most accurate predictor of conversion [21]

**Neuromyelitis Optica spectrum disorder (NMSOD):** It's a severe demyelinating white matter disease which is most likely accompanied by seropositive autoantibody to the aquaporin-4 (AQP4) water channel. It is often characterized by three features including optic neuritis, extensive myelitis in longitudinal manner, and positive anti-AQP4 antibody [22].

MRI is most preferred modality in case of NMSOD and requires evaluation of images from brain, orbit and spinal cord. Findings can be as follows:

**Orbit:** Swollen and hyperintense optic nerves on T2WI showed in (figure 07) along with enhancement on T1WI with contrast. Bilateral involvement and extension towards the chiasm (optic nerve crossing point) suggesting NMOSD [22]. In later stages, optic nerve atrophy with T2 hyperintensities can be noticed [23].

**Spinal Cord:**

Spinal Cord can show following disease features showed in (figure 09):

- Extensive involvement with hyperintense T2 signals spreading across at least three vertebral segments
- (Longitudinally extensive spinal cord lesion [2,22,23].
- Acute phase may commonly show cord swelling.
- Transverse myelitis where inflammation span across a short spinal cord segment occurs less frequently (14.5%) [23].
- Bright spotty lesions are a characteristic feature of NMOSD which are featured by high T2WI signals increased in intensity even compared to CSF and low T1 signal foci in central grey matter.
- MRI findings on T1, T2, and T1 contrast-enhanced (T1 C+) images for the spinal cord are also described:
- T1WI:
- Hypointense in later stages, indicating cord atrophy.
- T2WI:
- Hyperintense, often spanning across the length of three vertebral bodies.
- Involvement of central grey matter.
- Presence of bright spotty lesions.
- Patchy "cloud-like" contrast enhancement of bright T2 lesions.
- Thin ependymal enhancement resembling ependymitis.
- Lens-shaped enhancement on sagittal images [23].

MRI is indeed preferred modality in case of NMSOD but clinical correlation is central where patient does not present with typical triad in cases of seronegative AQP4-IgG + NMSOD or NMOSD in which there is AQP4IgG

unknown antibody status. International criteria for NMOSD warrants for specific characteristics including acute brainstem syndrome, symptomatic narcolepsy, area postrema syndrome, optic neuritis, acute myelitis, and acute diencephalic clinical syndrome with lesions typical to NMSOD in diencephalon on MRI and lesions typical to NMSOD along with symptomatic cerebral syndrome [22].

**Acute disseminated encephalomyelitis (ADEM):** ADEM is a white matter disease which is monophasic immune mediated disorder characterized by inflammation and demyelination. Often there is a history of preceding recent viral infection or vaccination [28,29]. ADEM can present with multiple asymmetric poorly defined lesions in both grey and white matter distributed bilaterally appearing on T2-weighted and FLAIR sequences. Additionally, open ring enhancement can often be seen on T1 (gadolinium) contrast-enhanced images showed in (figure 10). Diffusion restriction can also be noticed along the peripheries of the lesion. In view of the above features certain clinical considerations are essential to ascertain the diagnosis including preceding recent viral infection or vaccination. CSF analysis can also important as approximately of 50 % of the patients are identified to have anti-MOG (myelin oligodendrocyte glycoprotein) immunoglobulin G antibodies [2]. Magnetization transfer can help differentiate acute disseminated encephalomyelitis in comparison to multiple sclerosis because in ADEM normal appearing brain tissue has normal magnetization transfer ratio and normal diffusivity in contrast to multiple sclerosis where significantly decreased values are found. Follow-up imaging is essential in ADEM as it frequently shows resolution abnormal signal changes. However, development of new lesions is inconsistent as ADEM has monophasic course. Although complete resolution can occur in half of the patients but residual T2WI hyperintensities can be present indication gliosis and persistent demyelination [1,29].

**Progressive Multifocal leukoencephalo-pathy (PML):** Progressive Multifocal leukoencephalopathy (PML) is characterized by demyelination which occurs as result of reactivated John Cunningham virus (JC virus) infecting oligodendrocytes in patient with immunocompromised immune systems. The JC virus can infect the brain, and the most common way this shows up clinically is as PML [30]. There are three main situations where PML can develop:

- Immunocompromised state leading to JC virus infection and subsequent (PML).
- (PML-s-IRIS): This situation involves both PML occurs at the same time as immune reconstitution inflammatory syndrome (IRIS).
- (PML-d-IRIS): Patient with diagnosed with PML which is worsened by immune reconstitution.

**MRI Features (Figure 12):** It is usually noted to have multifocal, asymmetric, periventricular and subcortical involvement. Mass effect and contrast enhancement is not evident with PML [31]. Subcortical U-fibers involvement

is seen particularly in parieto-occipital [32]. The Lesions hypointense on T1WI. On T2WI, high signal lesions with multiple punctate high signal T2 lesions surrounding the main area (Milky Way Sign) [32,33]. Parieto-occipital abnormal signal lesions crossing splenium (Barbell sign) [33]. Cerebellar white matter lesion sparing dentate nuclei (Shrimp Sign) [34]. After consideration above MRI features it is highly suggestive to consider patients history for different immunocompromised situation. Progressive Multifocal Leukoencephalopathy (PML) was mainly seen in patient diagnosed with AIDS and very low CD4 counts (usually 50-100 cells/ $\mu$ L). This increase in non-HIV related PML is linked to several factors, including: Use of Immunosuppressive drugs post-transplant, inflammatory diseases like lupus (SLE) or sarcoidosis, Isolated CD4 lymphocytopenia) even without HIV, Certain monoclonal antibody therapies used for other conditions, such as natalizumab (for multiple sclerosis), efalizumab, and rituximab [34,35]. However, the final diagnosis can be confirmed by brain biopsy with 100% specificity.

**Osmotic demyelination syndrome:** It is acute demyelination disease on background of rapid osmotic changes typically due to quick correction of hyponatremia. MRI Features (Figure 13,14,15): Early Signs show diffusion restriction on diffusion weighted imaging particularly around the lower pons occurring in first 24 hours of symptoms onset such as quadriplegia [36]. The same region shows high T2WI signals and low T1WI signals after 2 weeks. This region typically shows a trident-shaped appearance. Occasionally, gadolinium enhancement can be seen similar to acute phase of multiple sclerosis (MS) [37]. Clinical evaluation is essential as presentation of osmotic demyelination syndrome has a clinically biphasic pattern. In first phase, electrolyte abnormality along with acute encephalopathy in patient. After correcting electrolytes abnormality rapidly, there is transient improvement in clinical condition is seen before deterioration to classic osmotic demyelination syndrome

features for next 2-3 days. Prominent feature is pontine involvement. Clinical features may include spastic quadriparesis, pseudobulbar palsy, altered conscious state, coma and death. It was mentioned in one article that serum sodium level correction should be 4 mEq/L to 6 mEq/L within 1 to 2 hours, with no more than 10 mEq/L correction within the initial 24 hours [38].

#### **Variants of multiple sclerosis:**

**Tumefactive multiple sclerosis:** A small number of cases in established multiple sclerosis may present with large rapidly demyelinating lesions showing characteristic contrast enhancement pattern described above. Tumefactive multiple sclerosis lesions may sometimes overlap with tumefactive demyelinating lesions which is a separate disease process keeping in mind the spectrum of diseases with similar features including multiple sclerosis, postinfectious demyelination/ADEM. However, histopathology may show more pronounced axonal damage in tumefactive multiple sclerosis compared to tumefactive demyelinating lesion [17]. Other lesions with similar appearance on imaging include primary brain neoplasm such as high-grade gliomas, metastatic malignancies in brain and abscess. Tumefactive multiple sclerosis can have features such as T1 low, T2 high intensity lesions with often no central diffusion restrictions and incomplete or open ring contrast enhancement showed in (Figure 16). However, ADC patterns at the edge of lesions shows significant diffusion restriction and can help distinguish between demyelinating diseases, abscess, and tumors [18]. MR spectroscopy is shown to be inconclusive when differentiating between neoplasms and tumefactive multiple sclerosis. Given the above mimics of tumefactive multiple sclerosis biopsies with histopathological correlation are often recommended for these atypical lesion to ascertain the diagnosis and underlying disease process as different treatment protocols and prognosis may ensue.

**Table 1:** Inclusion and exclusion criteria of articles

Inclusion or Exclusion	Population	Examples
Included	Articles discussing diagnosed cases of Multiple Sclerosis with different clinical presentations	Relapsing remitting Multiple sclerosis and radiologically isolated syndrome.
Included	Articles discussing diagnosed cases of Classic multiple sclerosis	(Charcot type)
Included	Articles discussing diagnosed cases of tumefactive multiple sclerosis.	Tumefactive Multiple sclerosis
Included	Article discussing diagnosed cases of Marburg type of multiple sclerosis	(Acute malignant)
Included	Article discussing diagnosed cases of Baló concentric sclerosis.	Baló concentric sclerosis.
Included	Article discussing diagnosed cases of Neuromyelitis Optica spectrum disorder	(NMSOD)
Included	Article discussing diagnosed cases of Acute disseminated encephalomyelitis	(ADEM)
Included	Article discussing diagnosed cases of Progressive Multifocal leukoencephalopathy	(PML)
Included	Article discussing diagnosed cases of Osmotic demyelination syndrome.	Central pontine myelinolysis due to quick correction of hyponatremia.
Excluded	Article discussing diagnosed cases of dysmyelinating disorders	Leukodystrophies

**Table 2:** Interventions

Included or excluded	Interventions	Examples
Included	Clinical correlation along with MRI and other imaging techniques	McDonald criteria used in diagnosis of multiple sclerosis
Included	Histopathological correlation with MRI imaging.	Histopathology to differentiate Tumefactive demyelination disorder

**Table 3:** Intervention and comparison

Intervention	Comparison	Example
Clinical presentation, accurate history taking and histopathological correlation with imaging	Solely relying on imaging techniques to rule out a diagnosis	McDonald's diagnostic criteria considering imaging findings along with clinical presentation

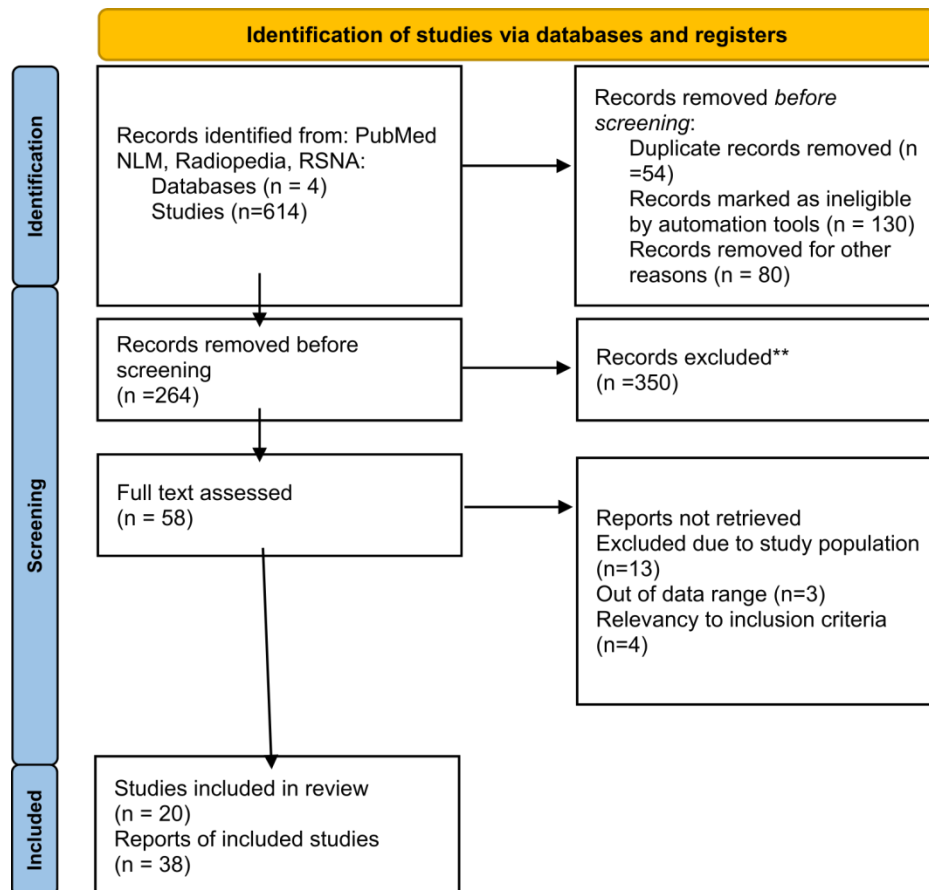
**Table 4:** Outcomes expected

Type	Outcome	Example
Primary	Timely and accurate diagnosis of demyelinating disorders	A timely detection of the inflammatory process in MS enables patients to start immunomodulatory agent with better treatment outcomes.

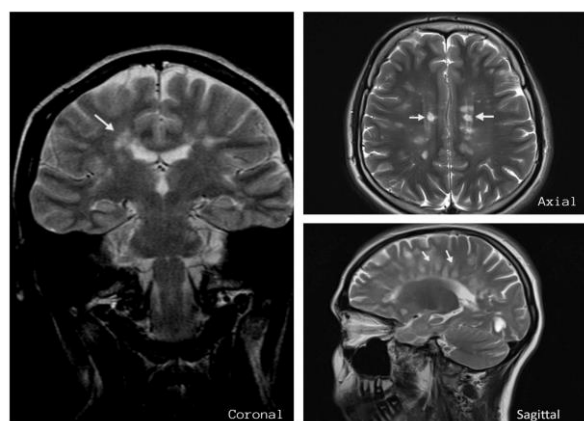
**Table 5:** Research plan

Status	Task	Description	Tool
Completed	Search and review existing relevant Systematic reviews	Search for and review existing relevant systematic reviews that answers a similar question.	PubMed Radiopedia
Completed	Look for group of relevant studies	Look for similar articles relevant to our review, to help in designing the Data collection and extraction.	Google scholar
Completed	Discussion writing	Write discussion, background and conclusion sections of the systematic review.	-

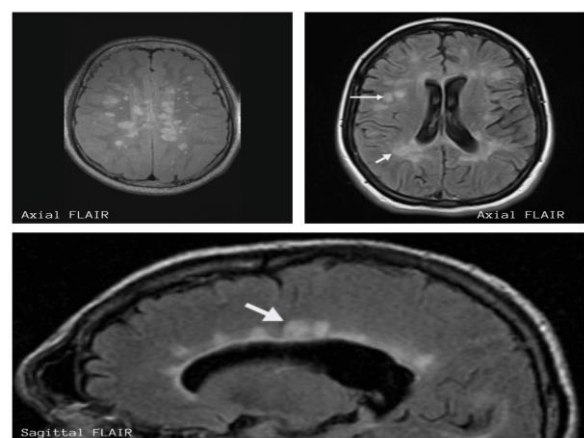
#### Prisma Flow chart:



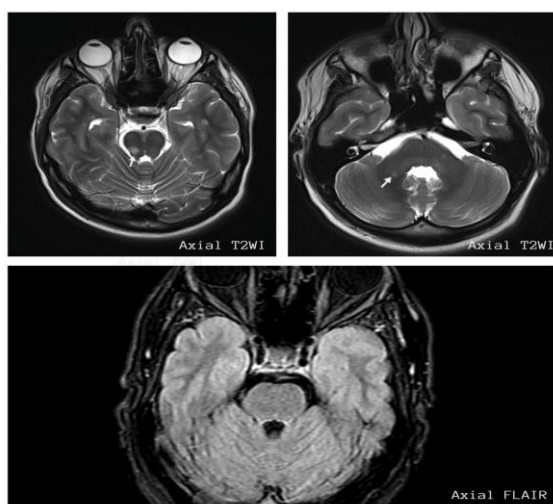




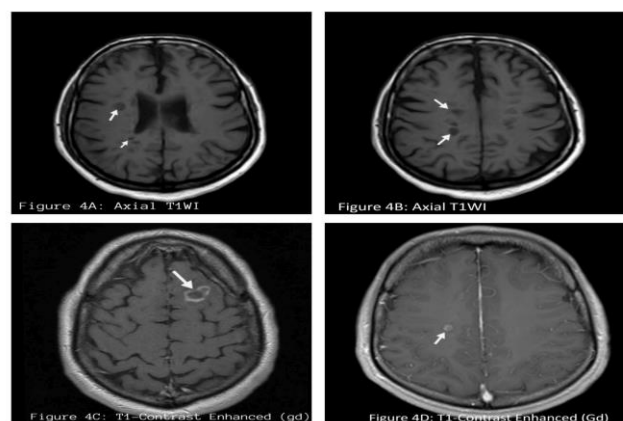
**Figure 1:** Images showing lesions in relapsing remitting MS. Standard T2 weighted images showing hyperintense lesions in particular configuration around corpus callosum termed as Dawson fingers.



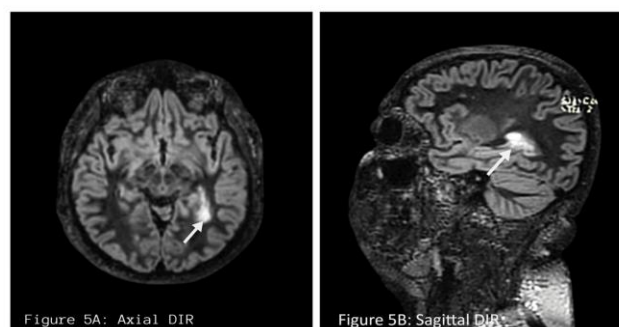
**Figure 2:** Axial and Sagittal FLAIR sequence images of a patient with Dawson fingers configuration and juxtacortical hyperintense lesions.



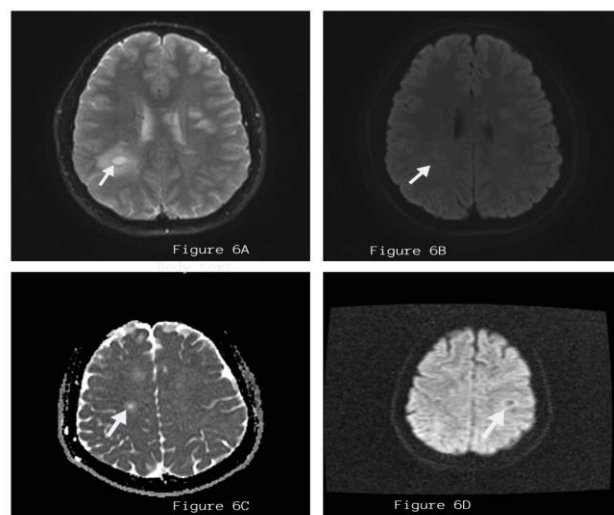
**Figure 3:** T2WI and FLAIR imaging of a subject showing superior sensitivity of standard T2WI compared to FLAIR in detecting posterior fossa lesions.



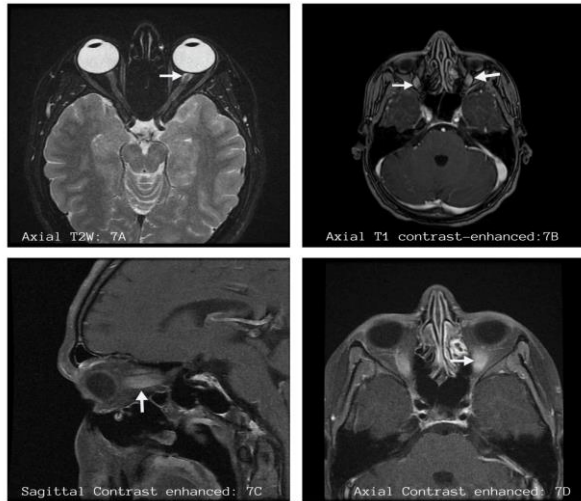
**Figure 4:** T1WI images showing hypointense lesions also termed as T1 black holes (4B) and bottom images (4C,4D) showing contrast enhancing lesions on T1-gadolinium (gd) contrast enhanced images.



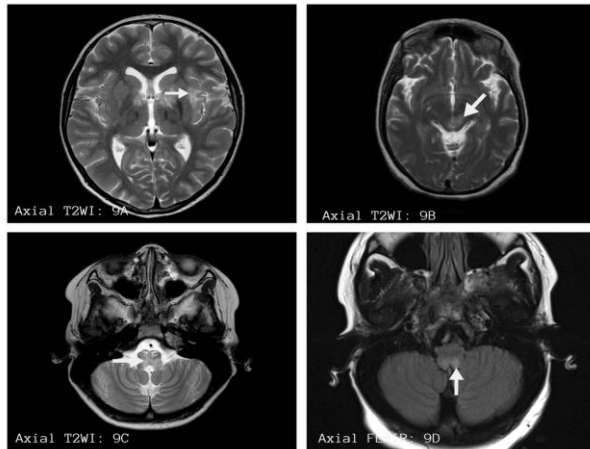
**Figure 5:** Double inversion recovery (DIR) uses two different inversion pulses and is handy when it comes to estimating of lesions load and to differentiate juxtacortical from mixed grey matter-white matter plaques.



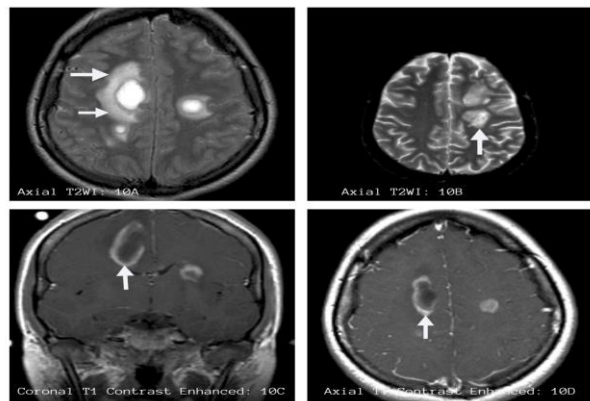
**Figure 6:** Diffusion weighted imaging can detect diffusion restriction and active plaques may show high or low signals on ADC sequence (increased or decreased diffusion)



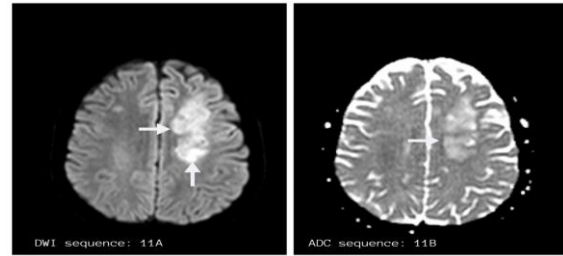
**Figure 7:** Figure (7A) showing hyperintense lesion of optic nerve T2WI and (7B,7C, and 7D) show contrast enhancement of T1 post-contrast images indicating optic neuritis in a patient with NMSOD.



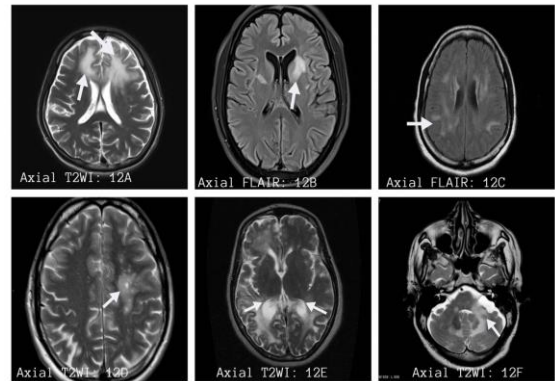
**Figure 9:** Images of a subject with diagnosed NMSOD showing T2WI hyperintense lesions in external capsule/ periventricular area (9A), periaqueductal grey matter (9B), and medulla oblongata (9C). FLAIR hyperintense lesion of area postrema shown in Figure (9D).



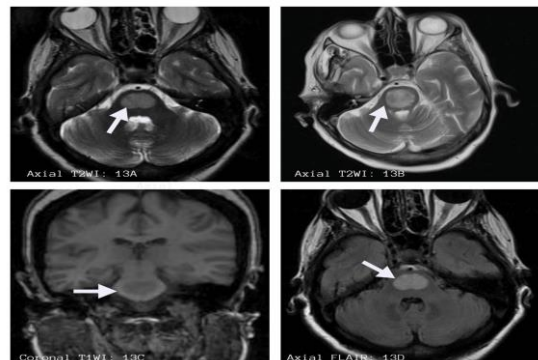
**Figure 10:** Images from a patient diagnosed with ADEM showing hyperintense lesions on Axial T2WI (10A) and (10B). Figure (10C) and (10D) T1 contrast-enhanced images showing open ring enhancing lesions.



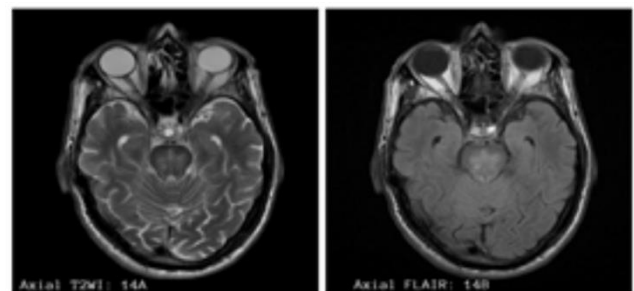
**Figure 11:** Images showing peripheral patchy diffusion restriction on DWI.



**Figure 12:** Figure (12A) showing hyperintense lesions on T2WI in a patient with ADEM. FLAIR Hyperintense signal lesions in (12B) and (12C). Typical signs for ADEM including milky way sign (12D), barbell sign (12E), and shrimp sign (12F).

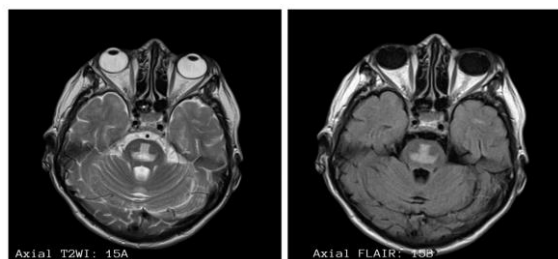


**Figure 13:** Images from a subject with osmotic demyelination syndrome showing T2WI and FLAIR hyperintense lesions on figures (13A), (13B), and (13D) respectively. T1WI hypointense lesions shown in (13C)

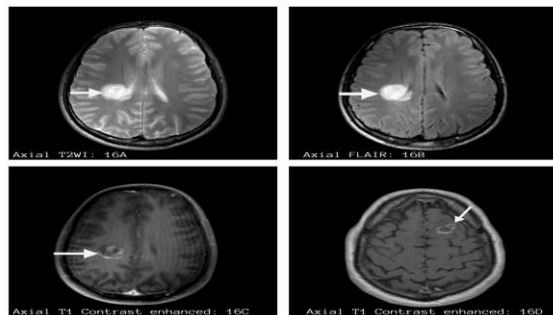


**Figure 14:** Images from a subject with osmotic demyelination syndrome showing hyperintense lesions in central pons on T2WI (14A) and FLAIR (14B).

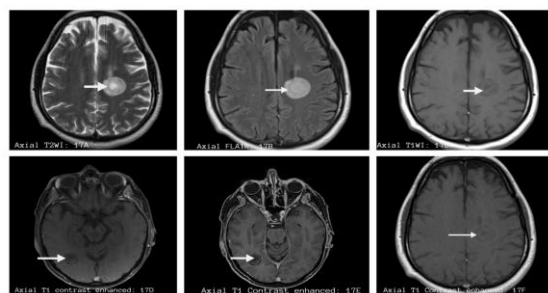




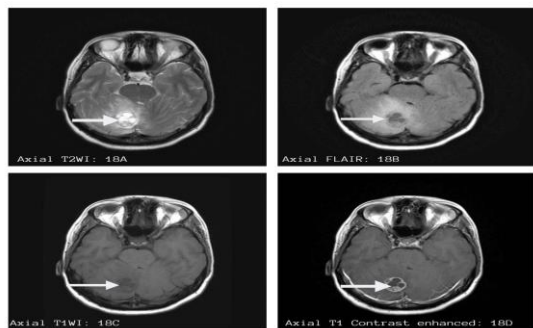
**Figure 15:** Images from a subject with diagnosed osmotic demyelination showing typical trident sign on T2WI and FLAIR sequences.



**Figure 16:** Patient with tumefactive multiple sclerosis showing T2WI (16A) and FLAIR (16B) hyperintense signal lesions in periventricular location. On T1 contrast enhanced images (16C) and (16D) only internal aspect of lesions is enhancing indicating incomplete ring enhancement.



**Figure 17:** Irregular concentric hyperintense lesions seen on T2WI (17A) and FLAIR (17B). Iso to hypointense lesion seen on T1WI (17C). Figures (17D), (17E), and (17F) showing peripheral ring enhancement in areas of active demyelination.



**Figure 18:** Images from a subject with Marburg multiple sclerosis showing confluent tumefactive hyperintense lesions on T2WI (18A) and FLAIR (18B). On T1WI lesions are iso to hypointense and ring enhancement seen on contrast enhanced image (18D).

**Baló concentric sclerosis:** It is an uncommon variant of multiple sclerosis which appears as rounded lesion with alternating layers of irregular concentric areas with hyper and hypo signal intensities on both T1WI and T2WI showed in (Figure 17) [19]. However, when differentiating from Marburg variant of MS and tumefactive demyelination it needs to be noticed that they lack characteristic concentric layering pattern. Clinical history is essential when differentiating Baló concentric sclerosis from Acute disseminated encephalomyelitis (ADEM) as the latter often has preceding viral infection or vaccination history [19].

**Marburg variant of multiple sclerosis:** Marburg variant is another rare variant of multiple sclerosis which results in rapidly progressing fulminant demyelination with often extensive MRI findings compared to rest of the variants of multiple sclerosis showed in (figure 18). Extensive confluent tumefactive demyelinating lesions with mass effect and incomplete/ c-shaped ring enhancement along with peripheral diffusion restriction can be detected [2]. However, despite the imaging findings clinical correlation and progression of the disease needs to be closely monitored as diagnosis can be subject to rapid deterioration of neurologic functions including hemiplegia, headaches, seizures and ‘altered mental status’ etc.

## DISCUSSION

The review shows that for diagnosis of multiple sclerosis the clinical information showed be assessed in terms of McDonalds criteria. Similarly, international criteria for NMOSD warrants for specific characteristics including acute brainstem syndrome, symptomatic narcolepsy, area postrema syndrome, optic neuritis, acute myelitis, and acute diencephalic clinical syndrome with lesions typical to NMSOD in diencephalon on MRI and lesions typical to NMSOD along with symptomatic cerebral syndrome. Follow-up imaging is essential in ADEM as it frequently shows resolution abnormal signal changes. The final diagnosis can be confirmed by brain biopsy with 100% specificity in diagnosing progressive multifocal leukoencephalopathy. Clinical presentation and rapid correction of electrolyte abnormalities along with MRI features in pons and brainstem are central to diagnosis of osmotic demyelination syndrome. Clinical history is essential when differentiating Baló concentric sclerosis from Acute disseminated encephalomyelitis (ADEM) as the latter often has preceding viral infection or vaccination history. In Marburg multiple sclerosis despite the imaging findings clinical correlation and progression of the disease needs to be closely monitored as diagnosis can be subject to rapid deterioration of neurologic functions including hemiplegia, headaches, seizures and ‘altered mental status’ etc. Several Confounding factors contribute to the disparity between clinical findings and MRI results. While may seem that increased lesion load in terms of demyelinating disorders correlates with worse clinical outcome but

clinical presentation may not accurately reflect MRI findings. MRI has limited ability to detect specific pathological changes, especially axonal loss and histopathological are preferable to get accurate measure of the disease process. Spinal cord damage, which is crucial in MS and NMSOD progression, is frequently overlooked in MRI assessments. MRI can underestimate the damage in NABT (normal appearing brain tissue) which can be a contradiction to clinical presentation. Recent progress in MRI techniques has highlighted the paradox of the clinicoradiological dissociation in MS. Utilizing MRI as one of the measures is essential to capture the full scope of demyelinating pathology, rather than relying on a single measure. Understanding the interplay between various dimensions of brain damage such as (NABT damage, residual brain volume, damage to spinal cord, and cerebral plasticity) and clinical judgement is central for the accurate use of MRI as an effective modality.

## CONCLUSION

The study underscores the importance of a comprehensive and multidimensional approach to diagnosis, predicting disease course, prognosis and monitoring of various demyelinating white matter disorders. Radiological investigations including MRI are also a useful tool when it comes to tracking the progress and efficacy of treatment of demyelinating disorders. Innovations in imaging sequences and post-processing techniques have significantly advanced the knowledge of demyelinating diseases, deepening insights into their pathology and progression. However, standard MRI techniques often lack specificity in detecting particular pathological changes or differentiate between different white matter disorders to utmost certainty, and there is frequently a weak correlation between radiological findings and clinical outcomes. While MRI is a vital tool, it cannot replace comprehensive clinical judgment that integrates all available information including clinical presentation, relevant history and histopathological investigations to pin point diagnosis. Imaging should supplement clinical decision-making, offering additional insights that support clinical evaluations. However, with advent of new imaging acquisitions, they will gradually be incorporated into clinical practice, enhancing the role of imaging in diagnosing and managing demyelinating diseases. Clinicians must remain aware of MRI's limitations and the necessity of corroborating radiological findings with comprehensive clinical assessments.

**Ethical Statement:** This systematic review was carried out based on guidelines and protocols provided for literature review and synthesis such as the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. Since this study was a literature review, no new data were collected on human participants or animals and therefore, no ethical approval was required. According to the institutional and

international ethical considerations no approval from ethical committee was needed for this particular research as it was not having any patient related data nor there was any interference with the human or animal subjects. The public databases were used for sourcing all the data used in this review and the studies incorporated in the review have already passed their own ethical approval processes.

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**Authors Contribution:**

- **RR:** Literature review, manuscript writing, searching articles and article processing as per PRISMA guidelines
- **HKM:** Plagiarism removal, formatting and grammar correction
- **HFS:** Article processing, images editing
- **NT:** Plagiarism removal and proof reading
- **SA:** Manuscript editing
- **MR:** Overviewing and Review conduction.

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