Brain and Spinal Cord MRI in Multiple Sclerosis: an Update

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ABSTRACT

Magnetic resonance imaging (MRI) plays an important role in the diagnosis of multiple sclerosis and has been incorporated into the McDonald diagnostic criteria for MS. In particular, for the exclusion of important differential diagnosis and comorbidities, new MRI markers have been established such as the "central vein sign". In addition to diagnostic purposes, the role of MRI in MS monitoring is becoming increasingly important, particularly for pharmacovigilance. This includes treatment efficacy monitoring, prediction of treatment response and safety monitoring. Quantitative MRI methods and ultra-high-field MRI offer the opportunity for the quantitative assessment of damage in normal-appearing brain tissue. However, the standardization of these techniques with the goal of implementation in clinical routine will be one of the major challenges in the near future.

Introduction

Multiple sclerosis (MS) is the most common chronic-inflammatory demyelinating disease of the central nervous system (CNS) [1]. In addition to clinical presentation and examination of the cerebrospinal fluid, imaging, in particular magnetic resonance imaging (MRI), plays an important role in the diagnosis and disease monitoring of MS [2, 3]. The increased relevance of MRI of the brain and spinal cord in the course of MS diagnosis has had a lasting effect on the design and modification of MS diagnostic criteria (McDonald criteria) [4]. The primary focus is on the detection of chronic inflammatory and neurodegenerative changes in the brain and spinal cord. Alternative pathophysiological theories such as the detection of chronic venous insufficiency have conclusively proved to be clearly wrong [5]. Large cohort studies also showed the prognostic value of MRI markers for long-term disability and the appearance of new clinical relapses. However, the overall prognostic value of MRI measures remains rather limited [6, 7]. Recently, international expert guidelines have clearly defined the role of MRI in diagnosis. Emphasis was placed on the need for standardization of MS imaging regarding image acquisition and examination intervals [8–10].

Compared to the long-established role of MRI in MS diagnostics, the relevance of imaging for observation or monitoring of the course of the disease had been long neglected. The introduction of new drug therapies with different and ever more effective mechanisms of action made apparent the importance and necessity of stringent treatment monitoring (pharmacovigilance) using MRI [11–14]. Accordingly, the previously mentioned international expert guidelines have been extended to include MRI follow-up of disease activity within the framework of the MS treatment [8–10].

Recent developments in MR imaging have significantly influenced the possibilities of improving in vivo detection of MS pathology. Such advances include the use of new pulse sequences, image acquisition at higher field strength and the use of quantitative MRI methods such as MR spectroscopy, diffusion tensor imaging and functional imaging [15–21]. These new and quantitative MRI methods allow us to investigate MS pathology in CNS structures that remain largely hidden by "conventional" MRI pulse sequences. Among other things, this affects examination of the cortical and deep grey matter as well as normal-appearing white (NAWM) and gray matter (NAGM) appearing on conventional pulse sequences [22–25].

► **Table 1** Standardized brain MRI protocol.

	Baseline MAGNIMS MRI (4, 5)	Baseline CMSC MRI (6)	Follow-up MAGNIMS MRI (4, 5)
Axial PD and/or T2-FLAIR/T2-weighted (T)SE	Yes	Yes, 3D sequence	Recommended
Sagittal 2D or 3D T2-FLAIR	Yes	Yes * *	No
2D or 3D T1-weighted after IV contrast *	Yes	Yes * * , before and after IV contrast	Yes
2D or isotropic T1-weighted 3D	Optional	Yes * *	Optional
2D and/or 3D DIR	Optional	No	Optional
Axial diffusion-weighted	Optional	No	No

* Standard contrast medium dose (single dose), 0.1 mmol/kg bodyweight

* * 3D acquisition before and after IV contrast

MAGNIMS = Magnetic Resonance Imaging in MS, CMSC = Consortium of MS Centers, PD = Proton Density, DIR = Double Inversion Recovery, IV = intravenous

► **Table 2** Standardized spinal cord MRI protocol.

	Baseline MRI	Baseline MRI
	MAGNIMS (4, 5)	CMSC (6)
Single-echo T2	Sagittal (when combined with STIR) (axial slices optional)	Sagittal, axial in region of lesions
Dual-echo PD/T2	Sagittal	Alternative to T2
STIR	Alternative to PD	Sagittal
2D or 3D T1 after IV contrast	Sagittal	Sagittal, optional
PSIR	Sagittal, optional	(PST1-IR)

MAGNIMS = Magnetic Resonance Imaging in MS, CMSC = Consortium of MS Centers, STIR = Short-Tau Inversion Recovery, PSIR = Phase Sensitive Inversion Recovery, PST1-IR = Phase Sensitive T1 Inversion Recovery, V = intravenous

The aim of this review is to provide an up-to-date overview of the importance of MRI of the brain and spinal cord during the diagnosis and monitoring of MS in the context of recently published expert guidelines.

The Role of Imaging in the Diagnosis of MS
Standardized examination protocol

For several years, there have been increasing national and international efforts to implement a standardized examination protocol. This is essentially due to the body of data that unequivocally demonstrates that image acquisition parameters (e.g., magnetic field strength, local resolution, pulse sequence selection, repositioning) can significantly affect the detection of MS lesions [26–28].

International expert groups, such as the European MAGNIMS Group and the Canadian/North American Consortium of MS Centers (CMSC), have a introduced a standardized protocol for imaging of the brain (► **Table 1**) and the spinal cord (► **Table 2**) based on recent developments in the field of MS imaging [4–6]. These suggestions are increasingly implemented by national specialist groups [29]. There are special issues regarding MRI examination of the optic nerve that should include dedicated pulse sequences as in a standardized acquisition protocol as suggested by international expert panel guidelines [30].

In Europe, there is consensus that imaging of the brain should take place preferably at 3 Tesla (T) due to the higher signal yield and improved detection of MS lesions compared to lower magnetic field strengths [17, 31]. A spatial resolution with a slice thickness of 3 mm and an in-plane resolution of 1 × 1 mm is recommended for two-dimensional (2D) pulse sequences. Regardless of field strength, isotropic 3D image acquisition is recommended, especially for the fluid-attenuated inversion recovery (FLAIR) sequence. This allows better contrast yield, multiplanar reconstruction, co-registration of follow-up examinations as well as the application of automated segmentation techniques [8, 32–35]. Although higher doses of contrast media reveal a greater number of enriched MS lesions, nevertheless a standard dose of 0.1 mmol/kg of body weight is recommended. This should be particularly noted in light of current discussions regarding the accumulation of certain gadolinium-based contrast media in certain deep gray matter brain structures such as the dentate nucleus[8, 36]. In the context of MS diagnosis, spinal cord imaging plays an especially important role. However, compared to brain imaging, imaging of the spinal cord is more demanding, mainly due to increased susceptibility to artifacts (pulsation of the heart and large thoracic vessels, cerebrospinal pulsations) [37]. In contrast to brain imaging, it has not been possible to show conclusively that a higher field strength of 3T results in an improved detection rate for spinal imaging [38]. Just as for cerebral imaging, a standard spatial resolution with a voxel size of 3 × 1 × 1 mm is recommended for 2D sequences. The benefit of contrast media for spinal imaging remains unclear and controversial. Only a small fraction of spinal MS lesions shows contrast enhancement and these lesions are also often clinically symptomatic [37, 39].

Imaging in the context of MS diagnosis criteria and differential diagnosis

Localization of MS lesions, the presence of contrast-enhancement, and the formation of new lesions in the course of the disease are crucial for MS diagnosis within the framework of the McDonald criteria regarding the demonstration of dissemination in space (DIS)

▶ **Table 3** 2010 Revision of McDonald criteria [4].

DIT	A new T2 or CM lesion compared to a previous examination without temporal limitation or a juxtaposition of asymptomatic CM-receptive and T2 lesions	Evidence meets the criterion of dissemination in time (DIT)
DIS	At least one T2 hyperintense lesion in at least 2 of the 4 following locations: periventricular, juxtacortical, infratentorial, spinal (a symptomatic brain stem or spinal cord lesion is ruled out)	Evidence meets the criterion of dissemination in space (DIS)

and in time (DIT) (▶ **Table 3**). By applying the 2010 revision of the McDonald criteria it is now possible to establish the diagnosis of MS in a patient with clinically isolated syndrome and simultaneous presence of lesions with and without contrast-enhancement in the case the contrast-enhancing lesions is asymptomatic. Otherwise, the criterion of DIT is considered to be fulfilled if a new typical T2w lesion or a new contrast-enhancing lesion is present in a follow-up exam without temporal limitation [4]. Typical imaging examples are shown in ▶ **Fig. 1**. Important criticisms of the McDonald criteria and recent study results resulted in a recently published work of the European MAGNIMS collaboration which offered an alternative proposal for the detection of DIS which does not differentiate between cortical/juxtacortical and symptomatic/asymptomatic lesions [40].

The spectrum of differential diagnoses of cerebral and spinal MS pathology is wide and heterogeneous. Please refer to a recently published overview for a detailed description and discussion of the differential diagnoses [41]. Differential diagnosis is also made more difficult by the fact that focal MS lesions can present with different
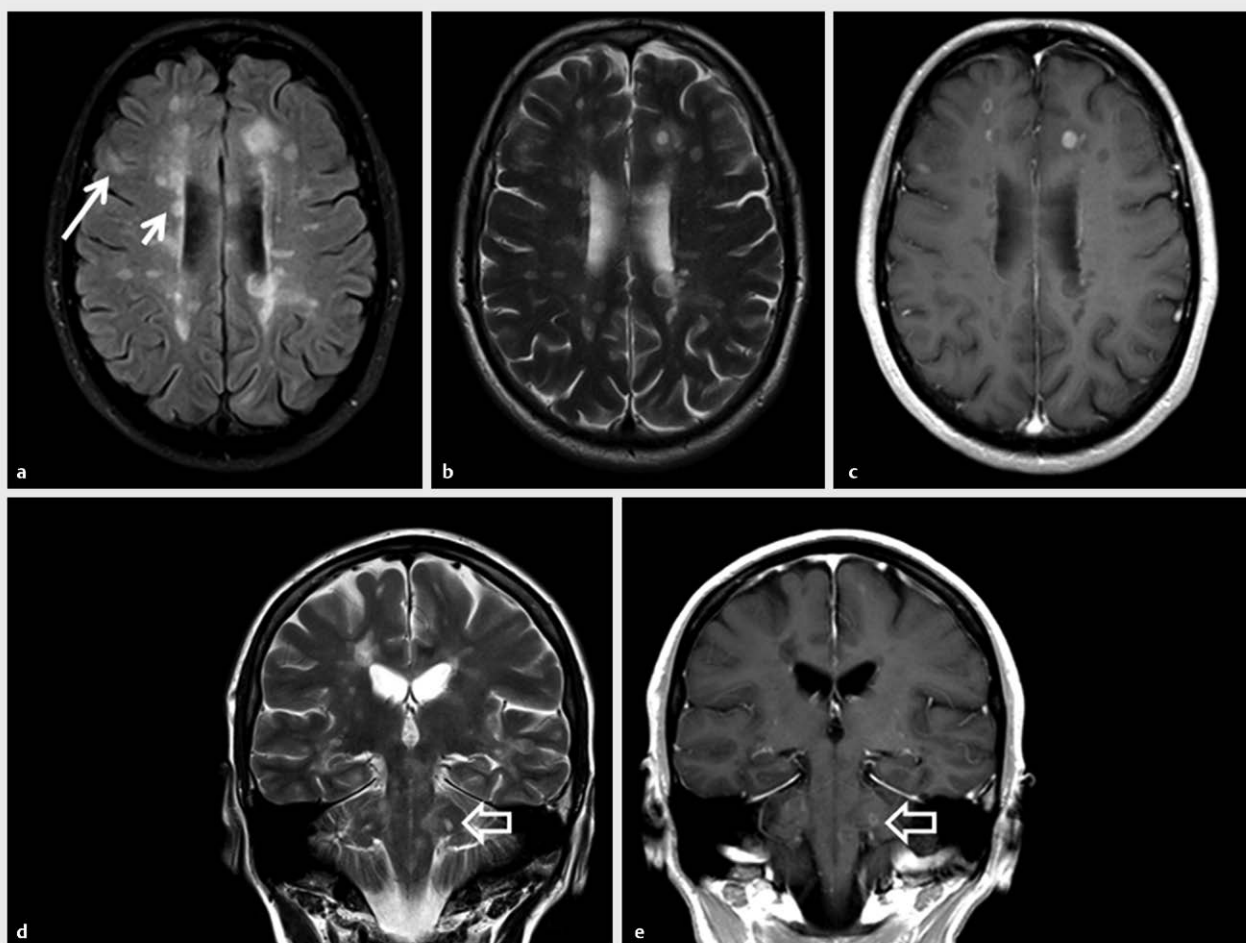
▶ **Fig. 1** Typical distribution pattern of acute and elderly inflammatory lesions in a patient with multiple sclerosis. **a** FLAIR sequence, **b** T2w sequence, **c** T1w sequence after administration of CM, **d** T2w coronal sequence, **e** T1w coronal sequence after administration of CM. All locations involved in the spatial dissemination with cortical/subcortical position (large arrow), periventricular position (small arrow) and infratentorial position (open arrow). There is a chain of lesions with and without barrier disruption or CM absorption (see **c** and **e**). The lesions not absorbing CM with noticeable T1w signal reduction are referred to as "black holes" which correspond to damaged parenchyma with myelin destruction.
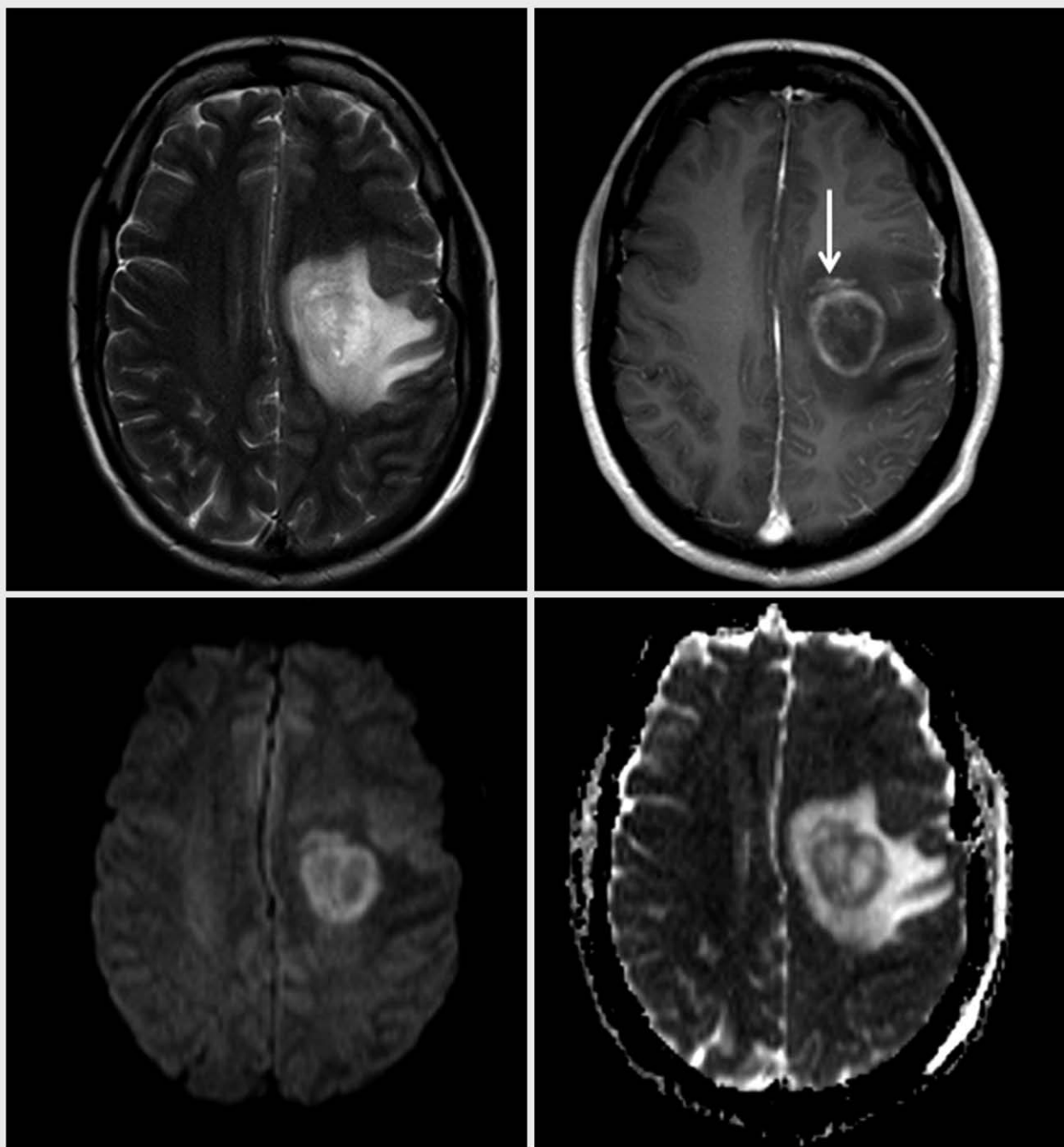
▶**Fig. 2** Transverse images of a large acutely inflammatory demyelinating lesion (top: T2w-TSE, T1w + CM; bottom DWI b1000 image and ADC). The patient was symptomatic with an arm-stressed hemiparesis, dysarthria, gait uncertainty, and blurred vision. Marginal and multi-layered CM absorption (arrow) of tissue alteration and mass effect, significant perifocal edema and marginal diffusion restriction with correspondingly low ADC values. Six months after this examination, edema was no longer present and the central tissue alteration had reduced to half its initial size. Individual foci with this signal pattern are probably signs of a tumorfactive demyelinating lesion (TDL). If this signal pattern is multi-focal, it is probably indicative of acute disseminated encephalomyelitis (ADEM). MS lesions this size are less likely.

forms and sizes, with different patterns of blood-brain barrier interference/contrastenhancement. In addition to the distinction of rare or atypical variants of idiopathic inflammatory demyelinating lesions (tumefactive demyelination (see ▶ Fig. 2)), "Balo-like lesions", hemorrhagic encephalomyelitis), emphasis is also put on

the differentiation of other inflammatory and vascular lesions [42, 43]. The spinal cord plays a decisive role in this process. In the vast majority of MS patients, the spinal cord (see ▶ Fig. 3) is frequently affected but it is rarely impacted by vascular diseases [44]. Due to the increased use of higher magnetic field strengths, the di-
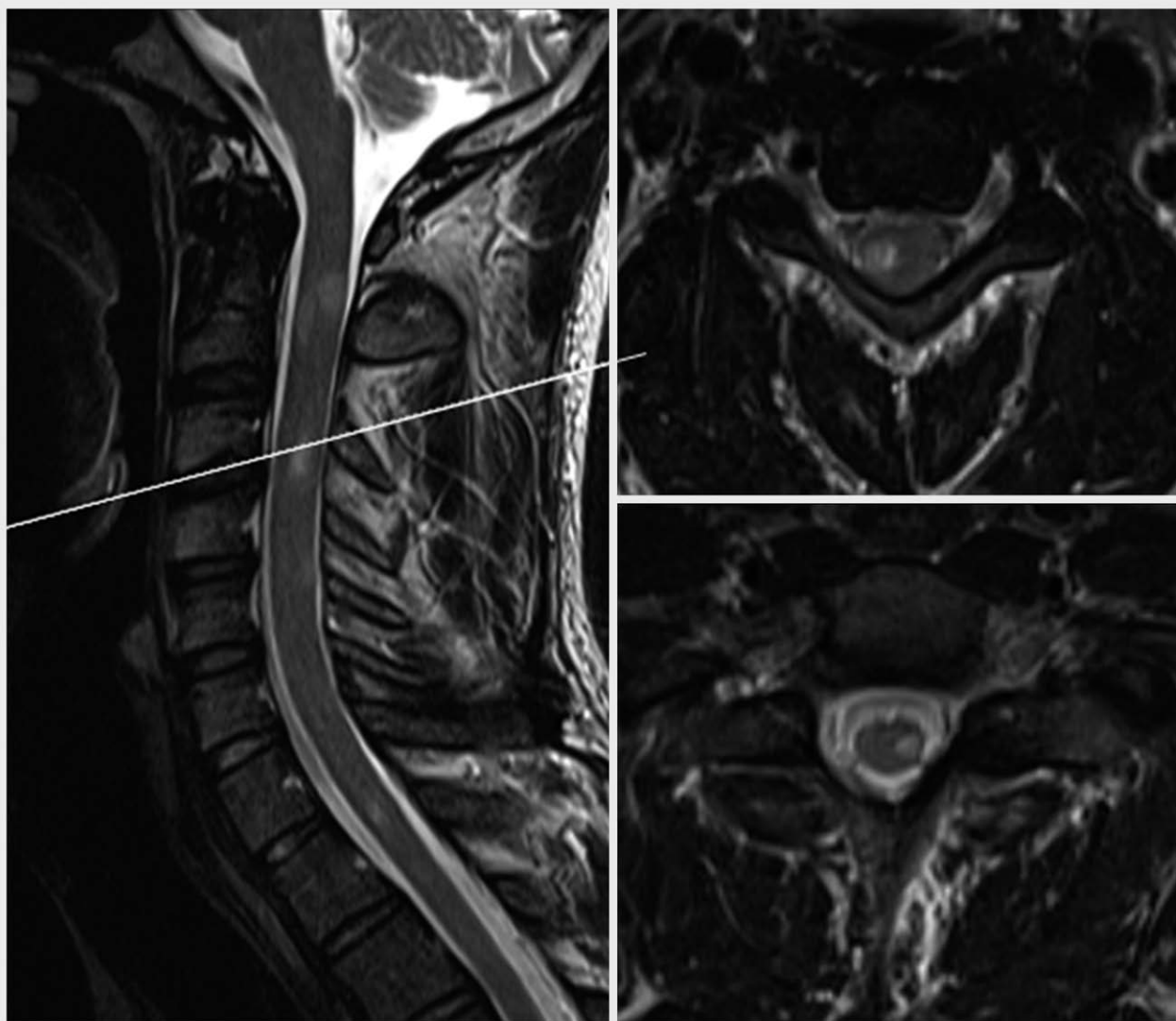
▶ **Fig. 3** Cervical lesion formations in multiple sclerosis with typical eccentric position recognizable in the two T2w transversal images. The sagittal T2w image shows several lesion formations which typically exhibit only a short supero-inferior expansion (average to max. 1.5–2 vertebral body heights). The white line in the sagittal image indicates the position of the superior transversal image).

agnostic attribute of the perivascular localization of MS lesions ("central vein sign") is becoming increasingly important (see ▶ **Fig. 4**). Recent data suggest that perivascular lesion distribution is useful in differentiating MS lesions from lesions of other MS differential diagnoses (e.g., vascular lesions, Susac's syndrome, neuromyelitis optica) [45–48]. Despite the enthusiasm, however, it should be noted that both the imaging and interpretation of the central vein sign are not yet completely standardized, but international expert groups are currently developing a standard [49].

New imaging technologies for the diagnosis of MS

Recent developments in structural imaging include, but are not limited to, 3D acquisition techniques and the use of (ultra) high-field MRI or a combination of both. A common application is the detection of cortical lesions. Due to increasing evidence that cognitive symptoms (e.g., epilepsy) in MS patients may be related to

cortical lesion load advances cortical lesion detection are gaining clinical relevance [50, 51]. Particularly relevant in this respect is the double inversion recovery (DIR) pulse sequence [31], see ▶ **Fig. 5**. Furthermore, the detection of leptomeningeal inflammation, which is also presumed to have particular clinical relevance with respect to the disability of MS patients, is becoming increasingly the focus of diagnostics using 3D sequences at higher magnetic field strengths[52]. However, the benefit of MRI regarding lesion detection (sensitivity, specificity) and the correlation with clinical parameters has been insufficiently investigated and is not clearly clarified [53].

In addition to standard sequences, further contrasts are used in the investigation and characterization of MS-induced parenchymal changes [54]. The following briefly describes some methods which can make a significant contribution to the detection of tissue damage and which can provide quantifying data.
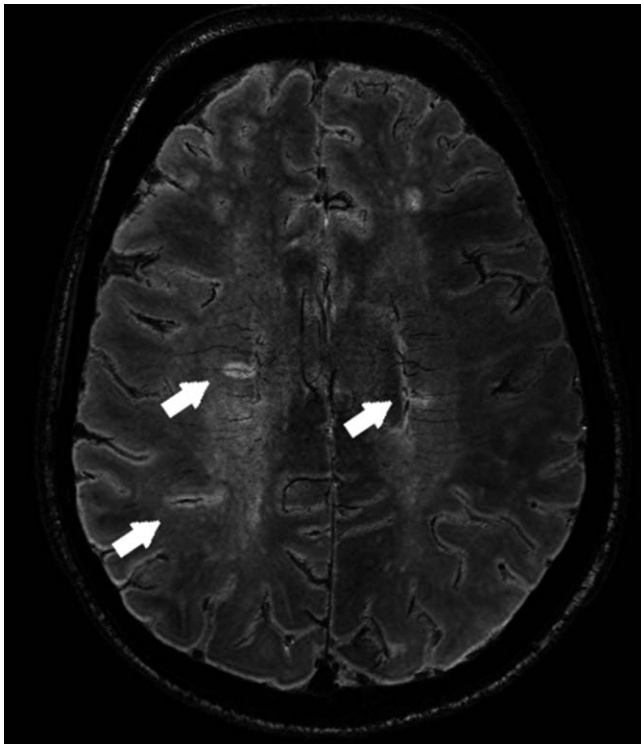
▶ **Fig. 4** Transversal FLAIR star sequence (FLAIR *) which combines the T2 weighting of a FLAIR sequence with the T2 * effect to detect a susceptibility effect. In this way the MS foci bordering on the medullary layer veins are clearly visible.

Normal T1w sequences can be combined with a magnetization transfer technique (MT) in which impulse modulation induces energy transfer between protons of macromolecules; these macromolecules thus contribute to the signal arising from the tissue [55]. Demyelination reduces this magnetization transfer effect and it is improved by remyelination. However, examination time is extended by this sequence modulation and the contrast between the cortex and the white matter is decreased, but a contrast enhancement effect can be improved. Therefore, the method should not be applied after administration of i.v. gadolinium based contrast, since the pure contrast effect can no longer be assessed due to the signal modulation of the MT effect. The magnetization transfer ratio (MTR) can be determined without contrast administration, since it results from the signal difference between images with and without MT pulse. However, gradient echo sequences are usually used for the calculation of MTR mapping due to the comparatively stronger MT effect. This method is not used in the clinical routine, since comparability is difficult between different sites, and the MT effect can also be influenced by non MS-related pathologies [56]. Although this method has long been established and is sometimes labeled "old fashioned", MTR is regaining relevance as a means of detecting remyelination of new neuroprotective MS drugs [57, 58]. Nevertheless, it should be noted that quantitative values in MTR maps are tissue markers and not specific for de- or remyelination.

The detection and quantification of iron deposits in MS lesions and deep grey matter is becoming increasingly important [59, 60]. These iron deposits can fluctuate as part of the temporal development of an MS lesion and thus contribute to its characterization

[59, 61]. In addition to the relatively new susceptibility-weighted imaging (SWI) method, its quantifying variant (quantitative susceptibility mapping = QSM) can also be used for this. These methods are highly sensitive to magnetic field disturbances. The SWI method also provides images with a contrast based on the phase shift of the spins in the voxels caused by field disturbances, thereby distinguishing between a diamagnetic magnetic field disturbance (e.g., calcification) and paramagnetic magnetic field disturbance (e.g., iron). In the QSM method, the susceptibility effects leading to a signal loss and the phase shifts are computed into one image; the QSM signal hyperintensity is proportional to the iron concentration in the tissue causing the field disturbance [59, 62]. However, the issue of the clinical relevance of iron detection and its quantification has not yet been conclusively resolved.

Widely used in stroke diagnosis, diffusion-weighted imaging, in which the signal obtained depends on the statistically possible water mobility in the tissue, can provide information about structural tissue changes. If, as in stroke diagnostics, the apparent diffusion coefficient (ADC) is calculated, it is usually possible to distinguish an acute/early subacute lacunar infarction with its ADC reduction from an MS lesion. The ADC values can also be used to assess tissue areas with seemingly normal appearance in the standard sequences, but more complex diffusion techniques such as diffusion-tensor imaging are more suitable for this. These more extensive diffusion measurements make it possible to determine the direction of the preferred water mobility as well as divide it into its longitudinal and transverse components. Changes in the longitudinal component indicate axonal changes and changes in the transverse component can be interpreted as myelin changes [63–66].

Another quantifying method is MR proton spectroscopy, which provides non-invasive information about metabolic components in the tissue. Due to their structure, the molecules to be determined lead to a defined displacement of the resonance frequency with their fingerprint-like arrangement of the intramolecular chemical bonds which can be detected and whose signal strength at this specific resonance frequency is essentially proportional to the concentration of the molecule in the tissue. The main metabolites are choline as a marker for cell membrane remodeling, creatine/phosphocreatine as a marker for the energy budget, N-acetyl aspartate (NAA) as a marker for neuronal integrety, lactate as an anaerobic glycolysis marker and myoinositol as a marker for activated glial cells. This method can be used on a standard clinical MRI system, but is usually employed only for research purposes and very special clinical issues (eg. differential diagnosis). Acute inflammatory foci may have elevated choline due to the increased cell membrane remodeling, whereas old MS foci are associated with a reduction of all major metabolites. A raised myoinositol level in apparently normal tissue may indicate an increased risk of developing MS in patients with a clinically isolated syndrome [20, 24, 67–69]. Advances in image acquisition (e.g., ultra-high-field MRI) open up a further development of MR spectroscopy and focus on other metabolites which play a decisive role in the pathophysiology of MS; these include GABA (γ-aminobutyric acid), glutamate and glutathione [70].

Even older MR methods, such as the quantifying determination of T1, T2 * and T2 relaxation times as well as their relaxation rates R (1/T), are again being given greater attention due to the increasing quality of the magnetic field homogeneities and sequence de-
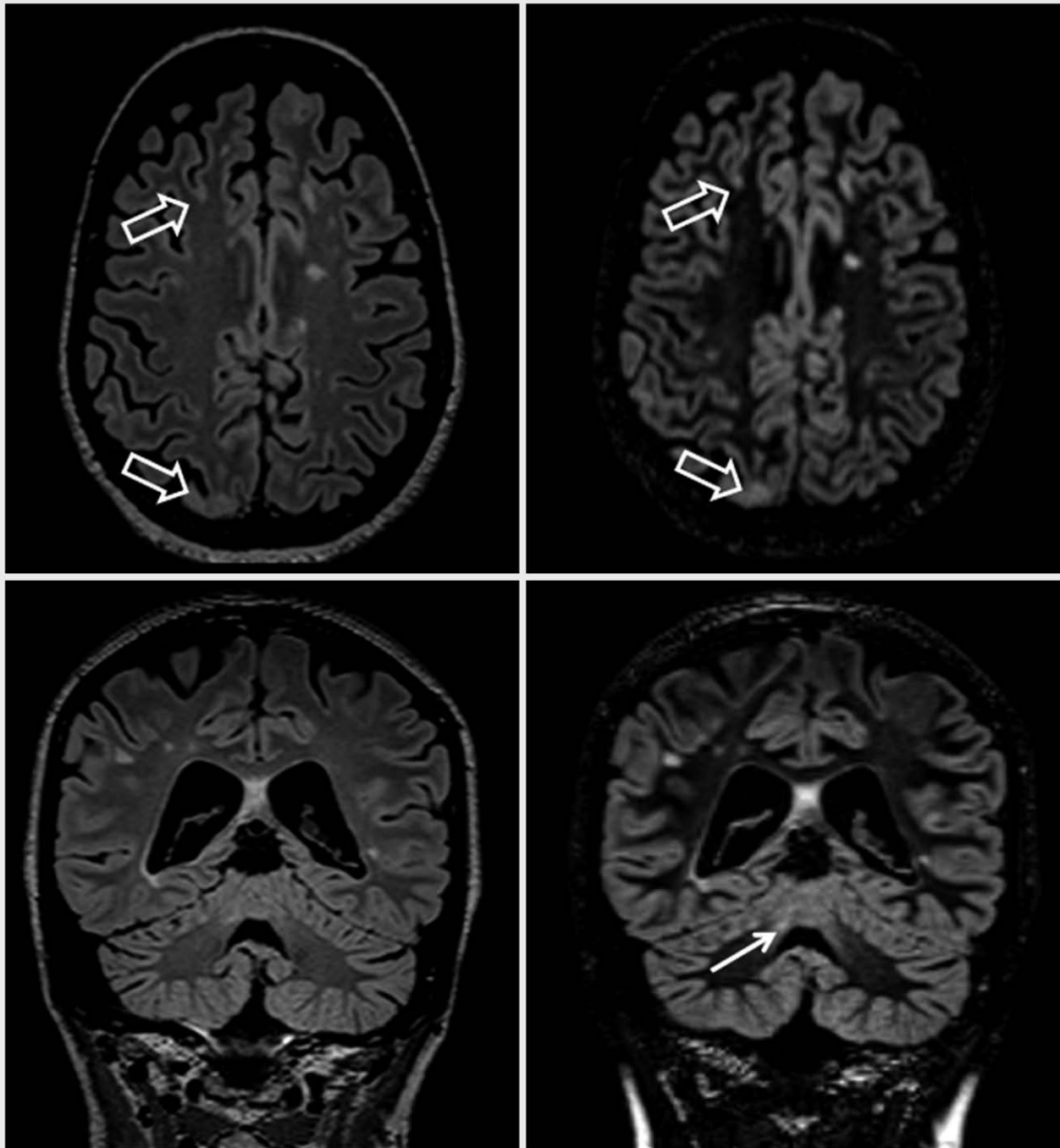
▶ **Fig. 5** Comparison of 3 mm thick slice reconstructions of a 3D FLAIR sequence (left) as well as a 3D double inversion recovery sequence. The recognizability of cortical/subcortical foci is significantly improved (see open arrow). Infratentorial recognizability can also be improved as it is shown by the lesion in the upper cerebellar stem (narrow arrow).

velopment. Thus it was shown that by determining relaxation parameters and calculating synthetic tissue maps, acute inflammatory lesions and their disruption of the blood-brain barrier could also possibly be identified without administration of contrast [71].

The Role of Imaging in MS Monitoring

Compared to its use in MS diagnostics, the role of MRI for MS monitoring purposes has been less investigated. Basically this concerns monitoring of MS treatment. Although the concept of pharmacovigilance is very often used in the context of safety monitoring, it

▶ Table 4 Significant findings of natalizumab-associated PML.

	Multi-sequence protocol for diagnosis and classification of PML
Size	Early stage: Focal lesion <1 cm
	Late stage: focal or multifocal lesion up to >3 cm
Location	Frontal > parieto-occipital > temporal; rarely: infratentorial or deep gray matter
	Subcortical white matter with inclusion of U fibers
	Cortical gray matter frequently also affected
Signal intensity	FLAIR and T2: hyperintense
	T1: isointense (early stage), hypointense (later stages)
	DWI: hyperintense
	T1 CM: contrast enhancement sign of inflammation in approx. 30 % of cases
Lesion characteristics	Sharp boundaries with cortex, indistinct boundaries with white matter
	Small T2 lesions (punctate pattern, "milky way")
	No atrophy, no mass

* It is recommended to perform this MRI screening protocol at 3–4 month intervals for patients with an elevated PML risk (high JC virus index, >2 years of natalizumab treatment).

also includes monitoring of MS disease activity and the prediction of treatment response. Standardized data collection is hindered by the fact that MS patients comprise a large and heterogeneous group. The spectrum of currently available MS therapeutics is broad, and the range of patients is heterogeneous with respect to treatment history and comorbidity. This likewise hinders the development of evidence-based guidelines on this issue.

Monitoring disease activity and treatment efficiency

MRI has been established as a method for observing inflammatory disease activity and is routinely used to monitor the effectiveness of MS treatment. Due to its high sensitivity, MRI can detect subclinical disease activity. Important and currently recommended MRI parameters for disease progression are contrast-enhancing as well as active (new or enlarging) T2 lesions [8–10, 72, 73]. The sensitivity of MRI with regard to the detection of these active T2 lesions within the scope of disease monitoring can be further enhanced by MRI subtraction techniques [74, 75]. Neurodegenerative changes occur very early in the course of the disease, although inflammatory changes are radiologically the forefront in the beginning of the disease [23, 76]. Neurodegenerative changes, such as atrophy and loss of cortical thickness, continue to accelerate during the course of the disease and correlate with clinical findings such as decline in cognition, fatigue, and disease progression [77–80]. Neurodegeneration is pathophysiologically very complex in MS and can be influenced by various factors such as alcohol consumption, smoking, dehydration, APOE * ε4 or cardiovascular comorbidity [81]. A very important factor is that anti-inflammatory therapies can lead to a clear reduction in brain volume in the first year of treatment, which then stabilizes

again in the second year of treatment. This phenomenon is referred to as "pseudoatrophy"; because of this, in addition to the difficulty of standardizing atrophy measurements (e.g., various hardware and software for post-processing and data analysis), interpretation of atrophy (eg, brain volume) data is challenging in clinical practice [77, 80, 81]. This has led to the recommendation that atrophy measurement cannot be used yet as a marker for the monitoring of MS patients [9].

In addition to volumetric methods, there are a number of other quantitative MRI methods with the help of which microstructural pathological changes in MS, especially in NAWM and NAGM, can be detected. These include functional MRI (fMRI), in addition to the previously-described MR spectroscopy, diffusion tensor imaging and the magnetization transfer method. Similar to atrophy measurement, the standardized application of these quantitative MRI methods in clinical routine is a challenge, and is not recommended at present because of the relatively long acquisition time required and the difficulty of adequate standardization [9]. A detailed description of all methods used for MS diagnostics and follow-up observation would go far beyond the focus of this review. Nevertheless, it should be stressed that these methods are of crucial importance for the newer generation of MS therapeutics which are primarily aimed at neuroprotection and remyelination. Conventional MRI markers such as active T2 lesions or contrast-enhancing lesions are not suitable for monitoring neuroprotection and remyelination. Animal experiments and initial human in vivo studies using diffusion tensor imaging, magnetization transfer and myelin water fraction imaging are promising [82, 83].

Prediction of treatment response

In recent years, several attempts have been made to establish a link between MRI parameters of MS disease activity before the start of a treatment and the success of that treatment. There are initial, but inconclusive, hints that disease activity measured by MRI can be helpful in identifying responders or non-responders. However, this strategy has not yet been proven in clinical practice and is therefore not recommended [84]. Likewise, the application of quantitative MRI methods, such as atrophy measurements or spinal imaging is difficult to standardize and not recommended for this clinical situation [9].

One established strategy is the detection of disease activity a few months after the start of treatment (reference MRI) and performance of a follow-up exam approximately 12 months after treatment start. The disease activity detected clinically (clinical relapses) and radiologically (active T2 lesions) between these two MRI examinations can be helpful in predicting the long-term treatment response and, consequently, to distinguish between responders and non-responders. It is important to realize that this concept of predicting treatment outcome has been established exclusively for interferon treatment in treatment naïve patients [85, 86] and is not entirely non-controversial or is not practiced in some countries (including due to resource problems). In addition, this concept has not been established for other (second line) MS drugs with other pharmacodynamic aspects and earlier or later treatment effects [73, 87].
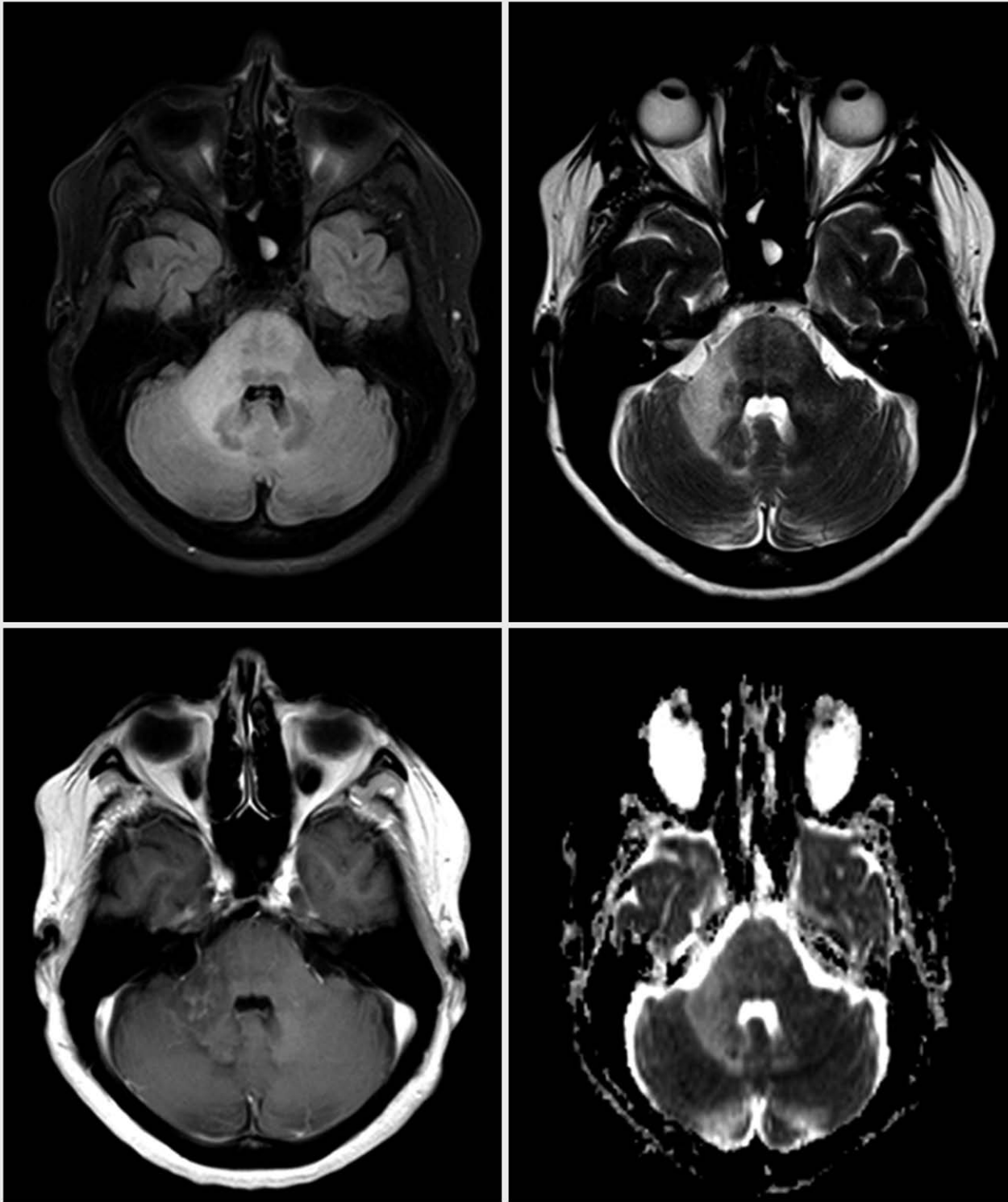
▶ **Fig. 6** Case of a patient with relapsing-remitting MS, in whom infratentorial PML occurred during natalizumab therapy (upper row FLAIR, T2w; lower row T1w + CM, ADC calculation). The T2w signal enhancements without massing effect can clearly be seen in the right cerebellar stem. Use of contrast resulted in an inhomogeneous T1w enhancement. The ADC values within the affected area are typically raised; depending on the stage of the PML, the boundary of a PML lesion can exhibit an ADC reduction.

▶ Table 5 Standardized MRI protocol for PML diagnosis in the course of MS pharmacovigilance.

	Multi-sequence protocol for diagnosis and classification of PML	PML screening protocol *
Axial T2 FLAIR	High sensitivity for PML detection	Recommended
Axial T2-weighted (T)SE	Detection of classical PML lesion pattern (e.g., small vacuoles, small T2 lesions in the vicinity of the actual PML lesion	Recommended
T1-weighted after IV contrast *	Determination of the severity of demyelination (T1 signal intensity) Sign of inflammation (contrast enhancement)	Not recommended
Axial diffusion weighting	Detection of active lytic infection with cell swelling and high signal intensity in DWI B1000 image	Recommended

* It is recommended to perform this MRI screening protocol at 3-4 month intervals for patients with an elevated PML risk (high JC virus index, >2 years of natalizumab treatment).

Safety monitoring

The introduction of the new generation of MS therapeutics with an improved efficacy profile and with a shift from immunomodulation to increased immunosuppression has made safety monitoring using MRI more important. The spectrum of safety monitoring includes the detection of clinically relevant non-infectious comorbidity, paradoxical MS disease activity and the identification of opportunistic infections [11–14].

In general, any morbidity of normal aging healthy individuals can also occur as comorbidity in MS patients, without any association with a particular therapy. This range of comorbidities includes, among others, vascular entities, neoplasms and inflammatory changes. An unwanted or unexpected MS disease activity is not per se a safety problem in MS treatment. Nevertheless, during MS therapy, so-called paradoxical, i.e., excessive, MS disease activity such as tumefactive demyelination can infrequently be observed. This phenomenon has been observed especially in some patients directly after the initiation of fingolimod therapy with tumefactive demyelinating lesions. It is currently unknown why a few MS patients react to this drug with an increase in inflammatory disease activity [88, 89].

The occurrence of opportunistic infections is a rare but clinically relevant and potentially life-threatening complication of immunosuppressive treatments. Progressive multifocal leukoencephalopathy (PML) is the most frequent opportunistic infection in immunosuppressive therapies in general and in MS therapy in particular [90]. PML arises from a reactivation of the JC virus, a neurotropic polyoma virus, which leads to a lytic infection of white (oligodendrocytes and astrocytes) and grey matter cells, resulting in irreversible demyelination and neuronal damage [91, 92]. It is described as a complication of several MS drugs (e.g., natalizumab, dimethylfumerate, fingolimod), with natalizumab-associated PML being of particular importance with respect to its frequency [93]. As of August 31, 2017, 746 cases of PML have been documented among MS patients receiving natalizumab therapy, a humanized antibody directed against α4 integrin [94]. MRI of the brain is of particular importance in the diagnosis of PML, since it (almost exclusively) affects the brain, but not the optic nerve or spinal cord [95, 96]. Compared to HIV-associated PML, natalizumab-associated PML shows particular imaging findings, especially the relatively frequent occurrence of contrast enhancement within or outside of PML lesions (▶ Table 4) [95–97]. Brain MRI is very sensitive to the detection of these lesions and can identify them at a very early stage while the patient has not yet experienced any clinical symptoms (presymptomatic or asymptomatic PML). Asymptomatic PML lesions are often found in the frontal lobe in the juxtacortical white matter and spreading into the cortical grey matter. However, they may occur more rarely in the deep grey matter or in the posterior fossa (see ▶ **Fig. 6**) [97, 98]. Asymptomatic PML patients have a better prognosis than patients with symptomatic PML at the time of diagnosis [99].

Therefore, European regulatory authorities and international expert groups currently recommend the use of a shortened MRI protocol in high-risk patients every 3–4 months looking for signs of PML (▶ **Table 5**) [9, 100, 101]. In individual cases, it may be very difficult to radiologically distinguish these small focal PML lesions from MS lesions or vascular changes, so that using MRI to support pharmacovigilance requires substantial neuroradiological expertise [102, 103]. Furthermore, other biomarkers such as the CSF JC virus index are currently being used to further support the radiological early diagnosis of PML [104, 105]. Other opportunistic infections are rather rare. Varicella zoster infections are well-documented for fingolimod therapy and very rare cases of Cryptococcal meningitis during natalizumab therapy [106, 107].

Conflict of interest

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