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Over the last decades, more and more new CNS-targeting radioligands have been developed, creating unique insight into the pathophysiology of neuroinflammation, demyelination, and remyelination. The applications of PET and hybrid PET-MRI have been primarily developed and investigated in different types of multiple sclerosis (MS), which are reviewed here.

Multiple sclerosis (MS) is a complex immune-mediated disorder, characterized by neuroinflammation, demyelination, gliosis, axonal degeneration, and neuronal loss. In 85% of cases, MS starts as a relapsing-remitting disease (RRMS) following an attack against the CNS by the adaptive immune system. This leads to formation of MRI-detectable, gadolinium-enhancing focal inflammatory lesions. Within 10–15 years following initial diagnosis, more than 60% of RRMS patients proceed to develop secondary-progressive MS (SPMS), in which relapses give way to relentless disease progression and accumulation of disability [1].

Disease progression is associated with activation of the local innate immune system within the CNS, and, gradually, white blood cell trafficking from the periphery into the CNS is reduced. Both resident microglia and blood-derived macrophages contribute to neuronal damage via release of pro-inflammatory cytokines and reactive oxygen species which lead to degeneration of neurons. Pathological studies have demonstrated that MS lesions in progressive disease rarely have features of acute inflammation. Instead, brain samples from patients with progressive disease harbor chronic active (smoldering or expanding) lesions, with microglial activation

at the edge of an otherwise burned-out plaque [2]. Alternatively, the chronic lesions are inactive, with no microglial activation at the plaque edge. In addition, widespread microglial activation is seen in areas surrounding the focal lesions, in the so-called normal-appearing white matter (NAWM) [3]. Therefore, microglial activation is assumed to contribute to the damage to the CNS induced by progressive MS [1].

Imaging Techniques

Over the last two decades, advanced structural and functional imaging techniques have provided unique insights into the pathogenesis of MS, contributing to improved clinical decision-making such as assessment of treatment response.

MRI: Structural Imaging

Currently, the most commonly used MRI marker for active inflammation in MS is enhancing white matter lesions, indicating disruption of the blood-brain barrier (BBB).

Histopathological studies have, however, shown that inflammatory brain pathology in MS is much more diverse and widespread than identified by conventional MRI techniques alone. Advanced techniques such as susceptibility-weighted imaging (SWI); perfusion imaging, both gadolinium contrast enhanced (DCE and DSC); arterial spin labeling (ASL) technique; and the use of ultrasmall superparamagnetic particles of iron oxide (USPIO) as an MRI contrast agent have advanced our understanding of these widespread, protean aspects of neuroinflammation in MS.

PET: Functional Imaging

Microglial activation is the central characteristic of neuroinflammation and a key element of neurodegeneration in MS. In vivo PET studies investigating microglial activation

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have focused on tracers binding to the 18-kDa translocator protein (TSPO), formerly known as the peripheral benzodiazepine receptor. Over the last decade, newer TSPO-targeting radioligands have been developed as biomarkers for neuroinflammation, creating a unique insight in the pathophysiology of neuroinflammation, neuronal dysfunction, demyelination, and remyelination.

The most frequently used TSPO radioligand is [11C]PK11195. Tracer uptake is increased in focal T2/FLAIR hyperintense MRI lesions, colocalizes with gadolinium-enhancing T1 lesions in relapsing-remitting MS, and is also increased in “normal”-appearing white and gray matter in MS patients as compared to healthy controls [2, 3]. There is also significant positive correlation of [11C]PK11195 uptake and disease duration, disability score, and brain atrophy. However, [11C]PK11195 has several disadvantages, including limited brain entrance, poor signal-to-noise ratio, and rapid decay due to the short half-life of [11C] ($t_{1/2} = 20.33$ min). Therefore, a wide range of second-generation TSPO radioligands have been developed. The main disadvantage of these new tracers is single-nucleotide polymorphisms (SNPs) in the TSPO gene (rs697) that result in a variation in binding activity between individuals, necessitating stratification by genotype [4].

Hybrid PET-MRI

Hybrid PET-MRI imaging improves *in vivo* visualization and quantification of the pleomorphic aspects of neuroinflammation, providing unique insight into the pathogen-

esis and therapy responsiveness in MS. This is particularly advantageous in SPMS (secondary-progressive MS), where hybrid PET-MRI may permit differentiation between active and inactive plaques. Increased PET tracer uptake is typically seen in chronic active (smoldering or expanding) lesions due to microglial activation at the edge of an otherwise burned-out plaque. Alternatively, the inactive chronic lesions with no microglial activation at the plaque edge demonstrate no tracer uptake [2]. In addition, widespread microglial activation is seen in areas surrounding the focal lesions, in the so-called normal-appearing white matter (NAWM) [3]. However, conventional MRI imaging alone cannot distinguish among these different types of lesions in SPMS patients, as the chronic active lesions usually do not demonstrate enhancement.

Furthermore, Rissanen et al. used PET imaging with a radioligand targeting the adenosine A2A receptor (A2AR)—a potent regulator of inflammation—to gain insight into the molecular alterations in normal-appearing white matter and gray matter of SPMS patients. They studied seven cases of SPMS and eight healthy controls and performed both MRI including DTI and [11C]TMSX PET [2]. Upon analysis of [11C]TMSX distribution volumes (VT), the SPMS patients had significantly increased [11C]TMSX activity with associated decreased fractional anisotropy on DTI in normal-appearing white matter compared with controls (Fig. 53.1). Importantly, these imaging biomarkers in SPMS patients were associated with higher expanded disability status scale (EDSS) scores, whereas the T2-lesion load did not correlate with EDSS.

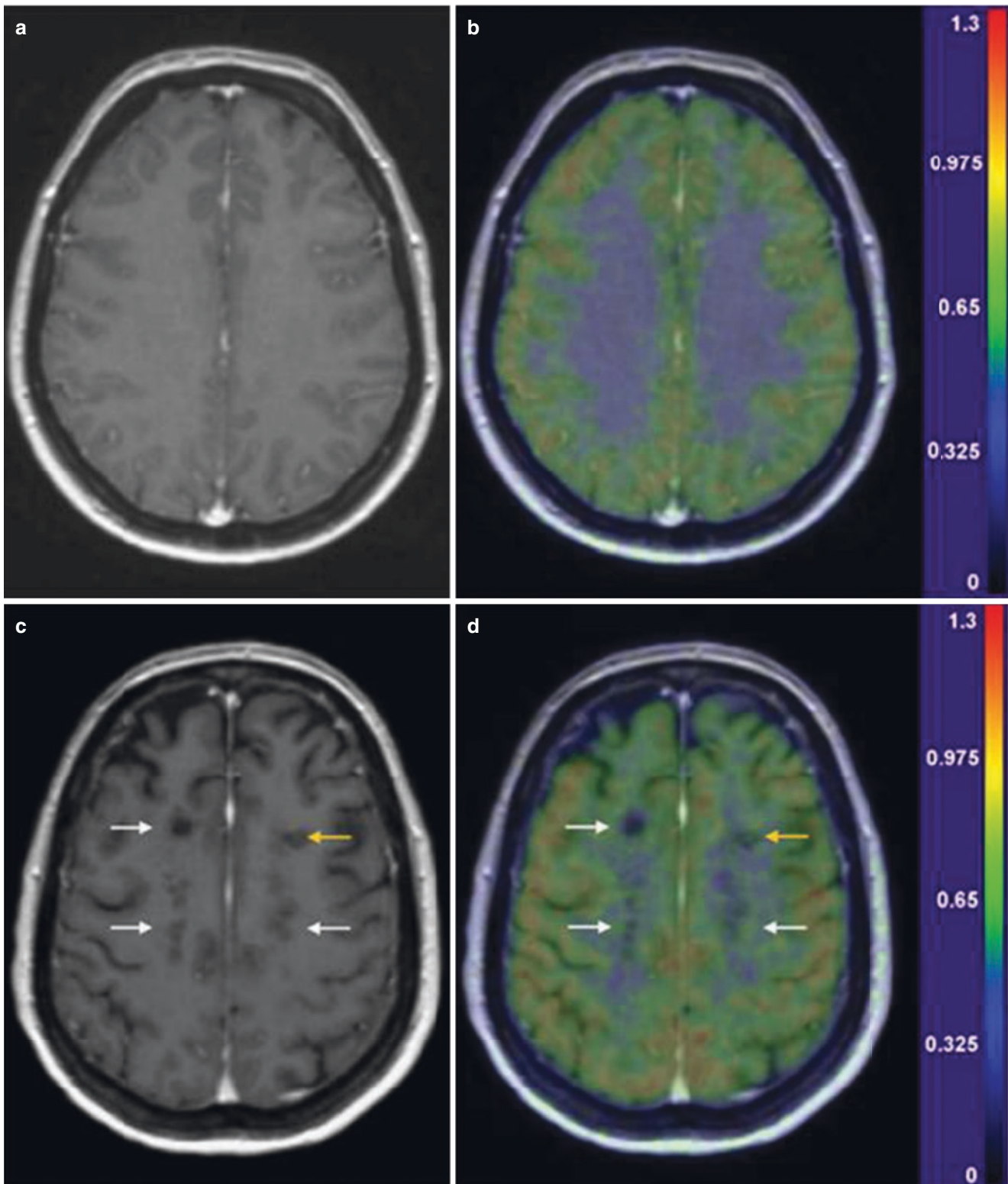


Fig. 53.1 Gd-enhanced 3DT1 magnetic resonance images (left column) and fusions of parametric [11C]TMSX-VT and 3DT1 MR images (right column) of a healthy 45-year-old woman (panels **a** and **b**) and a 48-year-old woman with secondary-progressive multiple sclerosis (SPMS) (panels **c** and **d**; disease duration of 6 years, EDSS 7.5) with transaxial views at corresponding supraventricular levels. The color

scale represents the [11C]TMSX-VT (ml/cm³). A pattern of increased [11C]TMSX binding can be seen around the T1 black holes bilaterally (white arrows) and within the slightly active plaque in the left frontal white matter (yellow arrow) in the SPMS patient compared with the lower, homogenous binding in the healthy control's white matter. (Reproduced with permission from Rissanen et al. [2])

References

1. Lassmann H, van Horssen J, et al. Progressive multiple sclerosis: pathology and pathogenesis. *Nat Rev Neurol*. 2012;8(11):647–56.
2. Rissanen E, Virta JR, et al. Adenosine A2A receptors in secondary progressive multiple sclerosis: a [¹¹C]TMSX brain PET study. *J Cereb Blood Flow Metab*. 2013;33(9):1394–401.
3. Moll NM, Rietsch AM, et al. Multiple sclerosis normal-appearing white matter: pathology-imaging correlations. *Ann Neurol*. 2011;70(5):764–73.
4. Owen D, Yeo A, et al. An 18-kDa Translocator Protein (TSPO) polymorphism explains differences in binding affinity of the PET radioligand PBR28. *J Cereb Blood Flow Metab*. 2012;32(1):1–5.