Review

Evaluation of the Utility of Hybrid PET/MR Neuroimaging in Inflammatory Demyelination and Encephalitis

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Review

Evaluation of the Utility of Hybrid PET/MR Neuroimaging in Inflammatory Demyelination and Encephalitis

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Abstract: With the increased availability of hybrid PET/MRI in recent years, this method is increasingly used for neuroimaging in clinical practice. It combines the advantages of MRI (including high-resolution imaging of intracerebral lesions and data provided from specialised MRI sequences) with the benefits of PET, which visualises functional alterations in the brain, as well as assessing the myelin quantity changes and the severity of inflammation. The use of PET/MRI may help to eliminate the limitations of MRI indicated in imaging demyelinating inflammatory diseases (such as low specificity in imaging demyelination and weak correlation of findings with clinical symptoms), as well as insufficient sensitivity in detecting lesions present in encephalitis. In addition to supporting the diagnosis of encephalitis, PET/MRI facilitates monitoring of the disease course and assessing the treatment efficacy of inflammatory demyelinating diseases and encephalitis, as well as evaluating the risk of multiple sclerosis relapse. Further multi-centre longitudinal studies are necessary to assess the real clinical potential of PET/MRI among patients with inflammatory demyelination or encephalitis. In addition to MS and AIE, these studies should also include other inflammatory demyelinating diseases (ADEM, NMO, NMOSD, and MOGAD) as well as encephalitis of viral and parasitic aetiology.

Keywords: PET/MRI; multiple sclerosis; inflammatory demyelination; AIE; encephalitis; neuroimaging

1. Introduction

Considering the diagnostic challenges in encephalitis (especially in seronegative autoimmune encephalitis (AIE)) - where it is not uncommon to find a normal magnetic resonance imaging (MRI) scan [1], as well as the low specificity of MRI in identifying the severity of demyelination and the activity of the inflammatory process and the poor correlation of imaged lesions with clinical signs in inflammatory demyelination, the use of a hybrid positron emission tomography/magnetic resonance imaging (PET/MRI) system may be of potential benefit to patients and clinicians [1–3]. This system allows to combination of the advantages of PET (i.e., the high specificity in imaging areas of demyelination, the possibility of assessing the severity of neuroinflammation, as well as detecting areas of hypo- and hypermetabolism) with the high resolution of MRI. The purpose of our paper is to evaluate the usefulness of hybrid PET/MRI in inflammatory demyelination and encephalitis in aspects of the diagnosis and differential diagnosis of these diseases, exploring their aetiopathogenesis, correlating imaging results with clinical symptoms, assessing the course of the disease and its prognosis, as well as evaluating the effectiveness of the applied treatment.

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2. Materials and Methods

PubMed, Web of Science and Scopus databases were searched using the combination (1) + (2) of following keywords: (1): 'PET-MRI' or 'PET/MRI'; (2): 'encephalitis', 'autoimmune encephalitis', 'parasitic encephalitis', 'viral encephalitis', 'inflammatory demyelination', 'multiple sclerosis', 'ADEM', 'NMO', 'NMOSD', 'MOGAD'. Our review includes studies published between 2004 and 2024 (until 01.10.2024). Papers that have not been published in English are excluded. We have included relevant articles in order to assess the utility of hybrid PET/MR imaging among patients with inflammatory demyelination and encephalitis as accurately as possible. Included papers were original research studies or clinical case reports that used hybrid PET/MRI or specialised software combining PET and MRI scans acquired from patients with inflammatory demyelination or encephalitis of autoimmune, viral or parasitic aetiology. We analysed these articles in terms of the diagnostic superiority of PET/MRI over other imaging modalities, its utility in monitoring the course of disease, its ability to correlate clinical symptoms with imaged lesions, assessing treatment efficacy and evaluating prognosis among patients with the mentioned diseases. We included data on: comparison of the sensitivity and specificity of PET/MRI in the diagnosis of inflammatory demyelinations and encephalitis with the sensitivity and specificity of other imaging modalities (MRI, PET and CT separately); correlation of results from clinical severity scales with tracer uptake levels in various brain areas; descriptions of the correlation of PET/MRI findings with patient prognosis; correlation between tracer uptake in different brain locations with lesions detected with MRI; as well as correlation between imaging results obtained with different tracers used on the same patients.

3. Inflammatory Demyelinating Diseases of the Central Nervous System

Inflammatory demyelinating diseases are a heterogeneous group of disorders with an acute or chronic inflammatory process underlying their aetiopathogenesis, which includes multiple sclerosis (MS), neuromyelitis optica (NMO), and neuromyelitis optica spectrum disorders (NMOSD), acute disseminated encephalomyelitis (ADEM) and myelin oligodendrocyte glycoprotein antibody-associated demyelination (MOGAD) [4]. To our best knowledge, PET/MRI has primarily been used in MS research, but its potential is also indicated in ADEM.

3.1. Multiple Sclerosis

MS is the most common non-traumatic cause of disability among young adults [5], with an incompletely elucidated aetiology that takes into account complex interactions between genetic, environmental and lifestyle factors [6]. Demyelination, central nervous system (CNS) inflammatory lesions and axonal degeneration are observed in the course of the disease [7]. MRI is the main diagnostic and monitoring tool for MS, which typically shows focal hypointense lesions on T1 sequences, while T2 and fluid-attenuated inversion recovery (FLAIR) sequences reveal hyperintense lesions [2,3]. The use of ultrahigh-field MRI and advanced MRI techniques (diffusion tensor imaging (DTI), magnetisation transfer imaging (MTI), diffusion-weighted imaging (DWI), and T2 relaxometry) may indirectly indicate demyelination [2,8], but these methods are not specific for quantifying myelin changes, as they are influenced by other conditions such as the presence of inflammatory infiltrate, oedema, intracellular and extracellular water or axonal damage [9]. A more specific method for quantifying myelin alterations is PET using radioligands that bind to myelin. In MS, PET can also be used to investigate the pathophysiology of CNS inflammation by utilizing markers of microglial activation, as well as to assess neuronal dysfunction [10]. The combination of PET and MRI in a PET/MRI hybrid system can provide a number of benefits by simultaneously obtaining complementary anatomical and functional data from both modalities.

3.1.1. Demyelination

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Studies indicate that radiolabels such as [^{11}C]-labeled Pittsburgh Compound-B ([^{11}C]PIB), [^{18}F]florbetaben and [^{18}F]florbetapir, which are used in the quantification of amyloid-β among patients with Alzheimer's disease [11], can also be used to quantify myelin content [12].

Studies using [^{18}F]florbetapir or [^{11}C]PIB and PET/MRI found that lesions visualised in T1/T2 MRI sequences among MS patients had a lower distribution volume ratio (DVR) compared to the DVR of the normal-appearing white matter (NAWM) of MS patients, as well as the white matter (WM) of healthy subjects [9,13,14], with no such relationship found by Zhang et al. in lesions smaller than 5 mm when comparing lesions of MS patients with NAWM [14]. Furthermore, the high intensity of T2 lesions was associated with lower DVR, and parametric DVR maps were more sensitive in imaging demyelination within smaller T2 lesions than parametric SUV maps. The lesions detected were characterised by a centripetal decrease in radioligand binding also involving the NAWM 2-8 mm around the lesions [9,13–15]. Nevertheless, research (except Pitombeira et al. [15]) has shown no differences between the averaged tracer uptake in the NAWM of MS patients and healthy subjects [13,14], which appears to be in opposition to alterations detected outside of lesions using advanced MRI techniques. However, it is worth noting that MRI techniques are not specific to alterations in myelin integrity, and the results are also affected by factors such as axonal damage or microglia activation present in the NAWM [9].

Although the study by Carotenuto et al. did not reveal gadolinium-enhanced (Gd+) lesions in any patient [13], Bodini et al. emphasise that Gd+ lesions were characterised by intermediate tracer uptake between the NAWM and the lesions observed in T2-weighted sequences, which may indicate that these lesions are affected by earlier stages of demyelination than T2-weighted MRI lesions [9].

The results of studies associating the degree of demyelination in specific CNS locations with clinical test outcomes are inconclusive. A study by Pitombeira et al. in 45 MS patients found that reduced DVR 11C-PIB values in the MRI lesions, corpus callosum and caudatum were associated with greater patient disability (as measured by Expanded Disability Status Scale (EDSS)) (Table 1.) [15].

Table 1. Correlations between neuroinflammation and demyelination tracer uptake levels, derived from hybrid PET/MRI in specific brain structures, with symptoms of disability and cognitive impairment in patients with multiple sclerosis. (EDSS - Expanded Disability Status Scale; 9-HPT - Nine-Hole Peg Test; SDMT - Symbol Digit Modalities Test; CVLT-II - California Verbal Learning Test II; BVMT-R - Brief Visuospatial Memory Test-Revised; 25-FWT - 25-Foot Walk Test; EF/IPS - Executive Functions/Information Processing Speed; PASAT - Paced Auditory Serial Addition Test; WLG - Word List Generation)).

	scale	radiotracer	quantitative metric	location of tracer uptake	correlation	research
	neuroinflammation					
disability	**EDSS**	^{11}C-PBR28	SUVR	cortex, thalamus, hippocampus, basal ganglia, NAWM, WM lesions	positive	Herranz et al. (2016)
				cortical lesions		Herranz et al. (2020)
				meningeal/parameningeal tissue		Herranz et al. (2024)
				cerebellar lesions and NAWM, cNAGM		Barletta et al.

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						(2020)
		(R)-[^{11}C]PK11195	V_T	cortical GM, cerebellar cortex, corpus callosum, caudatum, total T2-lesion, thalamus, NAWM		Pitombeira et al. (2022)
	9-HPT	(R)-[^{11}C]PK11195	V_T	cortical GM, cerebellar cortex, corpus callosum, caudatum, T2- lesions, NAWM	positive	Pitombeira et al. (2022)
cognitive impairment	SDMT	^{11}C-PBR28	SUVR	thalamus, hippocampus, NAWM	negative	Herranz et al. (2016)
				cortical lesions		Herranz et al. (2020)
				cerebellar NAWM		Barletta et al. (2020)
		(R)-[^{11}C]PK11195	V_T	corpus callosum		Pitombeira et al. (2022)
	CVLT-II BVMT-R	^{11}C-PBR28	SUVR	temporal and occipital cortex, cingulate, prefrontal cortex, thalamus	negative	Herranz et al. (2016)
	demyelination					
disability	EDSS	^{11}C-PIB	DVR	corpus callosum, caudate, total T2-lesion	negative	Pitombeira et al. (2022)
	9-HPT	^{11}C-PIB	DVR	**RRMS group only** caudate, lesions, corpus callosum	negative	Campanholo et al. (2022)
	25-FWT	[^{18}F]florbetapir	DVR	**RRMS group** T1/T2 lesions	negative	Carotenuto et al. (2020)
		^{11}C-PIB	DVR	**RRMS group only** lesions	negative	Campanholo et al. (2022)
cognitive impairment	SDMT	^{11}C-PIB	DVR	corpus callosum	positive	Pitombeira et al. (2022)
	EF/IPS (SDMT+PASAT+	^{11}C-PIB	DVR	**RRMS group only** caudate, thalamus, corpus callosum, cortical GM, WM, NAWM	positive	Campanholo et al. (2022)

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However, Carotenuto et al., in a study including 18 patients with relapsing-remitting MS (RRMS), found that DVR [^{18}F]florbetapir values in T1 and T2 lesions did not correlate with clinical test scores (including EDSS) except the Timed 25-Foot Walk (25-FWT) [13] (Table 1.). The authors suggest that an explanation for the inconsistency in results may be the greater precision of the 25-FWT test than the EDSS in detecting differences in patient disability. Conducted on 51 patients with MS, the Campanholo et al. study using hybrid PET/MRI and 11C-PIB to assess myelin imaging as a predictor of cognitive impairment and psychomotor speed revealed that data from advanced MRI techniques indirectly quantifying myelin in tissues - magnetization transfer ratio (MTR) (evaluated in the thalamus and corpus callosum) and DTI fractional anisotropy (FA) (in the thalamus and caudate) corresponded to differences in patient's cognitive status. DTI axial diffusivity (AD) and ^{11}C-PIB (DVR) in none of the regions studied were associated with cognitive function [16]. Only RRMS patients showed an association between ^{11}C-PIB and MTR uptake in certain areas and cognitive function and psychomotor speed (Table 1.). Although Zhang et al. did not show a correlation between the uptake of [^{18}F]florbetapir, FA, Mean Diffusivity (MD), AD, Radial Diffusivity (RD) in lesions and EDSS scores in the initial scan, they observed that a reduction in disability (decrease in EDSS) in a follow-up scan of the same patients was associated with a decrease in the global demyelination index, as well as a decrease in areas of demyelination in damaged white matter (DWM) lesions demonstrated with [^{18}F]florbetapir [14]. The authors suggest that a better reflection of clinical severity could be an assessment of remyelination, or the balance between demyelination and remyelination, rather than an assessment of demyelination only.

Du et al. indicate that radiomic data obtained with hybrid PET/MR using [^{18}F]florbetapir may help predict annual relapse rate (ARR) among patients with RRMS [17]. Their proposed multimodal model based on deep-learning using radiomic data from PET/MRI predicted the risk of MS recurrence with greater accuracy than single modality models based on PET or MR.

3.1.2. Neuroinflammation

Herranz et al. conducted a series of studies on the neuroinflammatory process in MS using PET/MR (two of them also used 7T MRI) with the highly specific expression marker TSPO (Translocator protein) - ^{11}C-PBR28 [18–20]. Patients with MS were reported to have a higher uptake of the radiolabel in the whole brain, especially in the cortex and cortical lesions, as well as in the deep grey matter (GM) and NAWM, compared to healthy subjects. In patients with secondary progressive multiple sclerosis (SPMS), higher whole-brain uptake of ^{11}C-PBR28 has been observed compared to those with RRMS. In SPMS, the frontal and parietal areas appeared to be the main areas most severely affected by neuroinflammation, while in RRMS, the occipital and temporal regions showed greater involvement [19]. Another study revealed increased neuroinflammation in cortical lesions (visualised on T2*-weighted 7T MRI sequences) in both forms of MS, while abnormally high TSPO uptake in the normal-appearing cortex was found only in patients with SPMS, which may suggest CNS inflammation and disease progression [20]. There was also a higher percentage of active lesions in SPMS (62%) than in RRMS (42%). Differences in the two forms of the disease were also observed by analysing the correlations between q-T2* (whose increase is associated with greater demyelination or iron loss) and ^{11}C-PBR SUVR (standardized uptake value ratio) in cortical lesions. In RRMS, a positive correlation was observed much more frequently. In contrast, in SPMS, the surface area of negatively correlated areas was larger, which the authors suggest could be related to inactive areas of chronic demyelination or tissue regeneration. The intensity of microglia activation in WM lesions in MS was relatively low. The reduction in cortical volume correlated with the severity of the neuroinflammatory response in the thalamus, which may suggest the spread of cortical pathology to the thalamus or the opposite.

The most recent of the studies, conducted on 49 MS patients, found that, in addition to the cortex, increased TSPO uptake was also present in the meninges (SUVR ^{11}C-PBR measured approximately 3 mm above the surface of the pia mater), indicating a role for meningitis in MS pathogenesis [18].

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Interestingly, patients treated with second-line disease-modifying drugs did not show an increase in TSPO signal in the meningeal and parameningeal tissue, which occurred in patients treated with first-line drugs. The authors indicate that the severity of neuroinflammation examined by hybrid PET/MR is related to the clinical symptoms of MS patients (Table 1.).

Barletta et al., using the same TSPO expression marker (^{11}C-PBR28) in PET-MRI and employing 7T MRI, demonstrated increased TSPO expression also in the cerebellum of MS patients [21]. Microglia activation, as measured by ^{11}C-PBR28 SUVR, was found to be higher in cerebellar lesions compared to the whole cerebellum of healthy subjects, as well as the SUVR of the NAWM and cerebellar normal appearing grey matter (cNAGM) of MS patients (even after exclusion of the perilesional area) was higher than in the WM and cortical GM, respectively, of controls. Interestingly, the presence or absence of treatment did not affect microglia activation. The intensity of microglia activation in the cerebellum was also shown to be statistically significantly associated with the degree of disability and cognitive impairment of patients (Table 1.).

Pitombeira et al., using PET/MR and two radiolabels - [^{11}C]PIB and the marker of innate immune cell activation - (R)-[^{11}C]PK11195 (TSPO)) in opposition to previous studies found no significant difference in the distribution volume (VT) of (R)-[^{11}C]PK11195 in any of the VOIs (Volume of Interest) tested between the MS patient group and the healthy subject group [15]. However, it should be noted that the first-generation TSPO tracer used is a lower sensitivity and specificity tracer than ^{11}C-PBR28, and the study used a volume-based analysis with predefined anatomical regions, which may have influenced the study results. However, the authors found diffusely increased uptake of TSPO in WM in patients with SPMS compared to healthy subjects and lower uptake of TSPO in some regions of WM in patients with RRMS compared to the healthy group. This study supports the correlation of the severity of neuroinflammation with the severity of clinical symptoms (Table 1.). Due to the observed lack of correlation between demyelination and innate immune cell activity in the anatomical regions studied, the authors suggest that these processes may be independent, which may account for the different disability profiles observed in patients with MS.

3.1.3. Summary

In conclusion, hybrid PET/MRI systems, thanks to the improved contrast between normal and damaged brain tissue, the possibility to better identify areas affected by neuroinflammation and demyelination, as well as the simultaneous provision of radiomic data from the two imaging modalities, is a promising neuroimaging technique that may be helpful in relating patients' disabilities and cognitive deficits, to specific regions of CNS neuroinflammation and demyelination, as well as in predicting MS relapses, or in assessing treatment efficacy.

The severity of neuroinflammation imaged by PET/MRI within lesions detected on MRI in the cortex, white matter and cerebellum, as well as in the whole cortex and cerebellum, NAWM, limbic system structures and meningeal tissue may correlate with symptoms of cognitive impairment and severity of disability in patients with MS. Highlighting the inconclusive nature of the studies published to date, we indicate that findings suggest that, particularly in RRMS patients, lower uptake of myelin-binding radioligand in T1- and T2-weighted MRI lesions, the corpus callosum and caudate may translate into increased motor impairment, while a correlation between cognitive impairment and increased demyelination in addition to these areas may also be observed in the thalamus, white matter and cortex.

However, further longitudinal studies on larger groups of patients are required, which, in addition to the processes of neuroinflammation and demyelination, will also take into account the remyelination process. The direction of further research should also include evaluating the efficacy of MS treatment with PET/MRI (including assessment of the severity of the inflammatory process involving the meninges), and it may also be helpful to use two radioligands (both a marker of demyelination and neuroinflammation - preferably second-generation TSPO) in the same patients to

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provide more insight into the pathogenesis of MS and to clarify the connections between these processes.

3.2. Acute Disseminated Encephalomyelitis

ADEM is an acute demyelinating inflammatory CNS disease involving multifocal areas of the WM, less commonly the GM and spinal cord, which typically shows a temporal association with infectious disease or vaccination [22,23].

Zhang et al. first described the use of hybrid PET/MRI using ^{18}F-florbetapir in imaging demyelination in a patient with ADEM [24]. The authors observed a significantly lower SUVR within the multifocal hyperintense lesions visualised on T2 FLAIR than on NAWM, indicating demyelination of these areas, which supported an accurate diagnosis of ADEM. PET/MRI was also used to assess response to treatment, visualising a reduction of lesions' hyperintensity and an increase in SUVR within the DWM, but this was still lower than normal, suggesting incomplete remyelination.

Lehaus et al. pointed out that PET/MRI using ^{18}F-fluoro-ethyl-tyrosine (^{18}F-FET), which is mainly used in neurooncology, was helpful in the diagnosis of ADEM in a patient with MRI findings suggestive of brain lymphoma [25]. Within the most extensive hyperintense lesion visible on MRI, heterogeneous ^{18}F-FET uptake was observed, while perivascular lesions showed low tracer uptake.

The above clinical case reports suggest that PET/MRI may be a useful diagnostic tool in ADEM to assist in the differentiation of ADEM from other disease entities, as well as help assess the efficacy of treatment. However, further studies on larger groups of patients are necessary to evaluate the real benefit of using this method among patients with ADEM.

4. Encephalitis

Encephalitis is most often caused by a virus, with Herpes Simplex Virus (HSV) being the most common. However, our review of the literature indicates that studies using PET/MRI have primarily focused on autoimmune encephalitis, which has become increasingly recognized [26].

4.1. Autoimmune Encephalitis

AIE refers to a heterogeneous group of central nervous system disorders in which the immune system generates autoantibodies that target neuronal surface antigens, synaptic receptors, and intracellular proteins. AIE presents with a wide spectrum of neurological manifestations, including cognitive impairment, motor dysfunction, psychiatric symptoms, epilepsy, and other potentially irreversible sequelae [27,28]. In addition to blood serum and cerebrospinal fluid (CSF) analyses, electroencephalography (EEG) and a clinical examination, neuroimaging plays an essential role in diagnosing and guiding therapeutic decisions in cases of known or suspected autoimmune encephalitis [27,29]. The most commonly employed imaging technique is brain MRI. While MRI is the initial and most frequently utilised imaging modality within the AIE patient demographic, it may manifest as normal or unremarkable in select patients [30]. Compared to traditional MRI, PET-MR is perceived to exhibit enhanced sensitivity in evaluating intracranial lesions. The concurrent utilisation of both methodologies can facilitate more expedient and precise diagnostic determinations [31].

Zhang et al., in their study using hybrid PET/MR, compared the diagnostic utility of ^{18}F-DPA-714 PET with conventional MRI in 25 AIE patients and assessed the correlation between TSPO PET uptake and clinical features [27]. The study revealed a positive detection rate of 72% for AIE when using ^{18}F-DPA-714 PET, as opposed to 44% for conventional MRI. Despite these figures, the statistical significance was not established. Among patients who showed alterations on PET as well as MRI, a greater range of abnormalities was often observed on positron emission tomography than on MRI, while in two patients, MRI showed lesions with a normal PET scan. Additionally, patients who experienced seizures demonstrated significantly elevated mean SUVR in the cerebral cortex than patients without seizures. In the group of 13 patients who underwent follow-up PET/MRI scans, 85%

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exhibited a reduction in ^{18}F-DPA-714 uptake, which co-occurred with an improvement in symptoms following immunosuppressive therapy. Similar observations were also described by Meng et al., who, using ^{18}F-DPA714 PET/MR in patients with seronegative AIE, found that 10/15 (67%) patients showed lesions on PET, while only 3/15 (20%) patients revealed lesions on MRI [32]. In contrast, four patients (27%) did not show lesions on either technique. The authors also found that increased tracer uptake correlated with the Clinical Assessment Scale for Autoimmune Encephalitis (CASE) score. Furthermore, the presence of ataxia was associated with a significantly higher SUVR in the cerebellum than in patients without ataxia. In 50% (5/10) of patients, a decrease in tracer uptake was found at follow-up. These findings indicate the potential usefulness of ^{18}F-DPA-714 PET in conjunction with MRI in the diagnosis of AIE (due to the complementary results of the two methods) and in the control of treatment efficacy.

Deuschl et al. studied the use of ^{18}F- fluorodeoxyglucose (^{18}F- FDG)-PET/MRI for diagnosing limbic encephalitis. Hybrid imaging detected abnormalities in 95% of patients (19/20), demonstrating superior sensitivity compared to single imaging modalities: MRI at 80% (16/20) and PET at 50% (10/20) [33]. Gallus et al. also highlight the diagnostic potential of [^{18}F]DPA-714 PET-MRI in autoimmune limbic encephalitis [34]. The authors found that increased uptake of the microglial activation tracer occurred asymmetrically in both mesial temporal lobes, with lateralisation of increased uptake corresponding to mesial temporal lobe lesions on FLAIR-MRI and abnormalities on the anterior temporal EEG.

A further study demonstrated the efficacy of FDG PET/MRI and PET/CT (computed tomography) in supporting the diagnosis of AIE among children as well [31]. Aydos et al. conducted a retrospective analysis involving six seronegative paediatric patients with a preliminary diagnosis of autoimmune encephalitis, only two of whom (33%) presented abnormalities on a previous MRI scan. The initial FDG PET and statistical parametric mapping method analysis findings were abnormal in all patients, with four cases exhibiting only hypometabolism. All patients had metabolic abnormalities in the temporal lobes. Additionally, visual and semiquantitative FDG PET findings revealed hypometabolism in extratemporal regions. One patient exhibited a hypermetabolic pattern in the right mesiotemporal lobe, while another patient demonstrated a mixed hypohypermetabolic pattern, characterised by hypermetabolism in the left mesial temporal lobe and hypometabolism in the left frontal, parietal lobes, posterior cingulate gyrus, and occipital lobe. Interestingly, the areas affected on MRI scan (mesial temporal lobes) corresponded to areas of hypermetabolism on PET imaging.

Simultaneous (^{18}F-FDG) PET/MRI was the sole factor facilitating the advancement toward a diagnosis of seronegative AIE in the case described by Taneja et al. [35]. PET/MRI revealed increased uptake of radiotracer in both temporal lobes and basal nuclei (caudate nuclei and putamen), while the MRI component revealed a mild FLAIR and T2 hyperintensity affecting the bilateral medial temporal lobes, including the hippocampus, as well as the bilateral basal ganglia and cingulate gyrus with minimal gyral thickening/swelling.

Other cases of AIE have been reported in the literature in which PET/MRI using ^{18}F-FDG and ^{18}F-DPA-714 played a key role in diagnosis. The authors indicate that the use of hybrid PET/MRI can increase diagnostic confidence in seronegative AIE cases [36]. They also describe patients with anti-NMDAR [37], voltage-gated potassium channel antibody [38], anti-Ma1 and anti-Ma2 [39], anti-LGI1 [40,41], anti-CASPR2 [40,42], against SOX1 [42], anti-GABA A receptor [43], and anti-DPPX [44].

In conclusion, employing a combined PET/MRI approach with quantitative analysis in cases of potential autoimmune encephalitis may be a very effective method to support diagnosis. Simultaneous PET/MRI offers an advantage over single-modality imaging techniques by combining high-resolution anatomic and functional information from MRI with metabolic information from PET within the same imaging session. The metabolic information derived from ^{18}F-FDG or ^{18}F-DPA-71 PET has been demonstrated to be particularly beneficial in patients with inconclusive or negative MRI results. The use of PET/MRI may also help to accelerate the diagnosis of AIE in seronegative

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patients. The observed abnormalities may also reflect clinical symptoms in patients with AIE and may prove useful in monitoring the course of the disease.

4.2. Viral Encephalitis

There is a shortage of studies and clinical case reports exploring using hybrid PET/MRI in viral encephalitis. To the best of our knowledge, the application of PET/MRI has been documented for viral encephalitis caused by HSV and Human Immunodeficiency Virus (HIV).

Schillaci et al., using special software, obtained ^{18}F-FDG PET/MRI images by overlaying images from separately acquired PET and MRI scans of a patient with Herpes Simplex Encephalitis (HSE) [45]. In addition to extensive areas of hypometabolism in the left temporal, parietal and occipital lobe coinciding with areas of hyperintensities in T1- and T2-weighted images, a decreased uptake of radiolabel in the left thalamus and striatum was demonstrated, which did not correspond with any alterations on MRI. A focal increased ^{18}F-FDG uptake was also observed in the inferior left temporal cortex, corresponding to a focal area of contrast enhancement in T1-weighted scans, which was described as a focal inflammatory process with meningeal vasodilation indicating active viral replication. The authors believe that the PET/MR images obtained may support the identification of active foci of inflammation, as well as the assessment of the prognosis and treatment of patients with HSE.

According to Pompanin et al., valuable data in terms of diagnosis, association of functional brain alterations with clinical symptoms, as well as assessment of treatment response and prognosis ^{18}F-FDG PET/MRI can also be provided in patients with HIV encephalitis [46]. In a patient with opsoclonus-myoclonus syndrome, the study showed extensive cortical hypometabolism (with sparing of the sensory-motor cortex bilaterally) and increased glucose uptake in the cerebellum, colliculus, red-nucleus and substance nigra, explaining the patient's symptoms. At follow-up 4 months later, there was a decrease in glucose uptake in areas of hypermetabolism and an increase in uptake in previously demonstrated regions of hypometabolism, which corresponded with clinical improvement.

4.3. Parasitic Encephalitis

There is a lack of work describing the use of hybrid PET/MRI in encephalitis of parasitic aetiology. However, based on the results of the independent use of ^{18}F-FDG PET/CT and MRI in neurocysticercosis, we suggest that hybrid PET/MRI is a method worth investigating, as it could have potential benefits (i.e., facilitating the diagnosis and differentiation of parasitic encephalitis, in which MRI findings alone may be atypical and suggest other diagnoses) [47].

5. Conclusions

PET/MRI utilizing relevant radioligands to image the severity of demyelination and inflammation, as well as indicate metabolic alterations within the brain, holds great potential for assisting clinicians in their practice. In the context of inflammatory demyelination, PET/MRI is valuable for monitoring disease progression, clarifying symptoms related to cognitive impairment, and evaluating the severity of disability in patients. Additionally, it may help assess treatment effectiveness and predict relapses in patients with MS. In cases of encephalitis, especially AIE, studies have demonstrated that PET/MRI is superior to other imaging modalities, particularly in terms of diagnosis and differentiation. This technique also has the potential to identify active foci of inflammation, monitor the progression of the disease, and evaluate response to treatment. To fully evaluate the potential of hybrid PET/MRI, further longitudinal studies are necessary involving larger groups of patients with inflammatory demyelinating diseases. These studies should encompass a range of conditions within this category, including ADEM, NMO, NMOSD, and MOGAD, in addition to multiple sclerosis. Additionally, more studies using PET/MRI in the field of encephalitis are

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needed, which should include research on viral and parasitic encephalitis in addition to the AIE studied so far.

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References

1. Hartung TJ, Bartels F, Kuchling J, Krohn S, Leidel J, Mantwill M, et al. MRI findings in autoimmune encephalitis. Rev Neurol (Paris). **2024**;180(9):895-907.
2. Hemond CC, Bakshi R. Magnetic Resonance Imaging in Multiple Sclerosis. Cold Spring Harb Perspect Med. **2018**;8(5).
3. Louapre C. Conventional and advanced MRI in multiple sclerosis. Rev Neurol (Paris). **2018**;174(6):391-7.
4. Höftberger R, Lassmann H. Inflammatory demyelinating diseases of the central nervous system. Handb Clin Neurol. **2017**;145:263-83.
5. Dobson R, Giovannoni G. Multiple sclerosis - a review. Eur J Neurol. **2019**;26(1):27-40.
6. Olsson T, Barcellos LF, Alfredsson L. Interactions between genetic, lifestyle and environmental risk factors for multiple sclerosis. Nat Rev Neurol. **2017**;13(1):25-36.
7. Garg N, Smith TW. An update on immunopathogenesis, diagnosis, and treatment of multiple sclerosis. Brain Behav. **2015**;5(9):e00362.
8. Filippi M, Rocca MA, Barkhof F, Brück W, Chen JT, Comi G, et al. Association between pathological and MRI findings in multiple sclerosis. Lancet Neurol. **2012**;11(4):349-60.
9. Bodini B, Veronese M, García-Lorenzo D, Battaglini M, Poirion E, Chardain A, et al. Dynamic Imaging of Individual Remyelination Profiles in Multiple Sclerosis. Ann Neurol. **2016**;79(5):726-38.
10. Niccolini F, Su P, Politis M. PET in multiple sclerosis. Clin Nucl Med. **2015**;40(1):e46-52.
11. Bao W, Xie F, Zuo C, Guan Y, Huang YH. PET Neuroimaging of Alzheimer's Disease: Radiotracers and Their Utility in Clinical Research. Front Aging Neurosci. **2021**;13:624330.
12. Auvity S, Tonietto M, Caillé F, Bodini B, Bottlaender M, Tournier N, et al. Repurposing radiotracers for myelin imaging: a study comparing 18F-florbetaben, 18F-florbetapir, 18F-flutemetamol,11C-MeDAS, and 11C-PiB. Eur J Nucl Med Mol Imaging. **2020**;47(2):490-501.
13. Carotenuto A, Giordano B, Dervenoulas G, Wilson H, Veronese M, Chappell Z, et al. [(18)F]Florbetapir PET/MR imaging to assess demyelination in multiple sclerosis. Eur J Nucl Med Mol Imaging. **2020**;47(2):366-78.
14. Zhang M, Ni Y, Zhou Q, He L, Meng H, Gao Y, et al. (18)F-florbetapir PET/MRI for quantitatively monitoring myelin loss and recovery in patients with multiple sclerosis: A longitudinal study. EClinicalMedicine. **2021**;37:100982.
15. Pitombeira MS, Koole M, Campanholo KR, Souza AM, Duran FLS, Solla DJF, et al. Innate immune cells and myelin profile in multiple sclerosis: a multi- tracer PET/MR study. Eur J Nucl Med Mol Imaging. **2022**;49(13):4551-66.
16. Campanholo KR, Pitombeira MS, Rimkus CM, Mendes MF, Apostolos-Pereira SL, Busatto Filho G, et al. Myelin imaging measures as predictors of cognitive impairment in MS patients: A hybrid PET-MRI study. Mult Scler Relat Disord. **2022**;57:103331.
17. Du S, Yuan C, Zhou Q, Huang X, Meng H, Chen M, et al. Deep learning-based PET/MR radiomics for the classification of annualized relapse rate in multiple sclerosis. Mult Scler Relat Disord. **2023**;75:104750.

 doi:10.20944/preprints202503.0716.v1

18. Herranz E, Treaba CA, Barletta VT, Mehndiratta A, Ouellette R, Sloane JA, et al. Characterization of cortico-meningeal translocator protein expression in multiple sclerosis. Brain. **2024**;147(7):2566-78.
19. Herranz E, Gianni C, Louapre C, Treaba CA, Govindarajan ST, Ouellette R, et al. Neuroinflammatory component of gray matter pathology in multiple sclerosis. Ann Neurol. **2016**;80(5):776-90.
20. Herranz E, Louapre C, Treaba CA, Govindarajan ST, Ouellette R, Mangeat G, et al. Profiles of cortical inflammation in multiple sclerosis by (11)C-PBR28 MR-PET and 7 Tesla imaging. Mult Scler. **2020**;26(12):1497-509.
21. Barletta VT, Herranz E, Treaba CA, Ouellette R, Mehndiratta A, Loggia ML, et al. Evidence of diffuse cerebellar neuroinflammation in multiple sclerosis by (11)C-PBR28 MR-PET. Mult Scler. **2020**;26(6):668-78.
22. Esposito S, Di Pietro GM, Madini B, Mastrolia MV, Rigante D. A spectrum of inflammation and demyelination in acute disseminated encephalomyelitis (ADEM) of children. Autoimmun Rev. **2015**;14(10):923-9.
23. Javed A, Khan O. Acute disseminated encephalomyelitis. Handb Clin Neurol. **2014**;123:705-17.
24. Zhang M, Liu J, Li B, Chen S. F-florbetapir PET/MRI for quantitatively monitoring demyelination and remyelination in acute disseminated encephalomyelitis. EJNMMI Res. **2019**;9(1):96.
25. Lohaus N, Mader C, Jelcic I, Reimann R, Huellner MW. Acute Disseminated Encephalomyelitis in FET PET/MR. Clin Nucl Med. **2022**;47(2):e137-e9.
26. Ellul M, Solomon T. Acute encephalitis - diagnosis and management. Clin Med (Lond). **2018**;18(2):155-9.
27. Zhang M, Meng H, Zhou Q, Chunyu H, He L, Wang H, et al. Microglial Activation Imaging Using 18F-DPA-714 PET/MRI for Detecting Autoimmune Encephalitis. Radiology. **2024**; 310(3):e230397.
28. Nissen MS, Ryding M, Meyer M, Blaabjerg M. Autoimmune Encephalitis: Current Knowledge on Subtypes, Disease Mechanisms and Treatment. CNS Neurol Disord Drug Targets. **2020**;19(8):584-98.
29. Graus F, Titulaer MJ, Balu R, Benseler S, Bien CG, Cellucci T, et al. A clinical approach to diagnosis of autoimmune encephalitis. Lancet Neurol. **2016**;15(4):391-404.
30. Sanvito F, Pichiecchio A, Paoletti M, Rebella G, Resaz M, Benedetti L, et al. Autoimmune encephalitis: what the radiologist needs to know. Neuroradiology. **2024**;66(5):653-75.
31. Aydos U, Arhan E, Akdemir ÜÖ, Akbaş Y, Aydin K, Atay LÖ, et al. Utility of brain fluorodeoxyglucose PET in children with possible autoimmune encephalitis. Nuclear Medicine Communications. **2020**;41(8):800-9.
32. Meng H, He L, Chunyu H, Zhou Q, Wang J, Qu Q, Hai W, Zhang Y, Li B, Zhang M, Chen S. ^{18}F-DPA714 PET/MRI as a potential imaging tool for detecting possible antibody-negative autoimmune encephalitis: a prospective study. J Neurol. **2024**; 271(12):7592-7604.
33. Deuschl C, Rüber T, Ernst L, Fendler WP, Kirchner J, Mönninghoff C, et al. 18F-FDG-PET/MRI in the diagnostic work-up of limbic encephalitis. PLoS ONE. **2020**; 15(1):e0227906.
34. Gallus M, Roll W, Dik A, Barca C, Zinnhardt B, Hicking G, et al. Translational imaging of TSPO reveals pronounced innate inflammation in human and murine CD8 T cell–mediated limbic encephalitis. Science Advances. **2023**; 9;9(23)
35. Taneja S, Suri V, Ahuja A, Jena A. Simultaneous 18F- FDG PET/MRI in Autoimmune Limbic Encephalitis. Indian Journal of Nuclear Medicine. **2018**;33(2):174-6.
36. Tamayo Carabaño D, Acevedo Bañez I, Lojo Ramírez JA, García Morillo JS, García Solís D, Jiménez-Hoyuela García JM. F-FDG PET for the diagnosis and assessment of treatment response of autoimmune limbic encephalitis. Rev Esp Med Nucl Imagen Mol (Engl Ed). **2023**;42(3):196-7.
37. Crimì F, Camporese G, Lacognata C, Fanelli G, Cecchin D, Zoccarato M. Ovarian teratoma or uterine malformation? PET/MRI as a novel useful tool in NMDAR encephalitis. In Vivo. **2018**;32(5):1231-3.
38. Day BK, Eisenman L, Black J, Maccotta L, Hogan RE. A case study of voltage-gated potassium channel antibody-related limbic encephalitis with PET/MRI findings. Epilepsy Behav Case Rep. **2015**;4:23-6.
39. Meng H, Zhou Q, Chen S. Anti-Ma encephalitis masquerading as Wernicke encephalopathy. J Clin Neurosci. **2020**;79:160-162.
40. Roll W, Bauer J, Dik A, Mueller C, Backhaus P, Räuber S, et al. [18F]DPA-714-PET-MRI reveals pronounced innate immunity in human anti-LGI1 and anti-CASPR2 limbic encephalitis. Journal of Neurology. **2024**;271(6):3653-9.

 doi:10.20944/preprints202503.0716.v1

41. Cecchin D, Zoccarato M, Anglani M. Case 39: Limbic Encephalitis. Clinical Nuclear Medicine in Neurology: an Atlas of Challenging Cases: Springer International Publishing; **2021**. p. 199-202.
42. Shen R, Shen D, Zhou Q, Zhang M, Chen S. Antibody-mediated autoimmune encephalitis evaluated by. Brain Behav Immun Health. **2022**;26:100535.
43. Vacchiano V, Giannoccaro MP, Napolitano RP, Liguori R, Allegri V, Rinaldi R, et al. Combined brain positron emission tomography/magnetic resonance imaging in GABAA receptor encephalitis. European Journal of Neurology. **2019**;26(10):e88-e9
44. Zhou Q, Zhu X, Meng H, Zhang M, Chen S. Anti-dipeptidyl-peptidase-like protein 6 encephalitis, a rare cause of reversible rapid progressive dementia and insomnia. J Neuroimmunol. **2020**;339:577114.
45. Schillaci O, Chiaravalloti A, Travascio L, Floris R, Simonetti G. (18)F-FDG PET/MR in herpes simplex virus encephalitis: A case study. Rev Esp Med Nucl Imagen Mol. **2014**;33(4):249-50.
46. Pompanin S, Cecchin D, Cagnin A. Opsoclonus-myoclonus syndrome in HIV encephalitis: Treatment and PET/MRI functional changes. Revue Neurologique. **2022**;178(3):268-9
47. Jolepalem P, Wong CY. Neurocysticercosis on 18F-FDG PET/MRI: co-registered Images. Clin Nucl Med. **2014**;39(1):e110-3