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REVIEW

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Amyloid PET scan diagnosis of Alzheimer's disease in patients with multiple sclerosis: a scoping review study

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Abstract

Background Multiple sclerosis (MS) is an autoimmune disease affecting the central nervous system. This study aimed to evaluate the advantages and disadvantages of a positron emission tomography (PET) scan method for diagnosing Alzheimer's disease (AD) in MS patients with no clinical symptoms or early-onset AD.

Main text To identify potentially relevant documents, we systematically searched international databases from 2000 to 2021. We abstracted data on article characteristics, ID/country, study, design, population, type of tracer, and outcomes. The primary outcomes were mean amyloid tracer standardized uptake value relative (SUVr), AD diagnosis in MS patients, and the tracer's uptake. Secondary outcomes were the megabecquerel amount of tracer and tracer side effects. Nine studies were finally entered into our research for review. Among the studies included, two studies used 18F-florbetaben, six of these used 11C-Pittsburgh compound B (11C-PiB), and in two studies (18)F-florbetapir (18F-AV1451) was used for imaging. Data from 236 participants were included in this study (145 MS patients, 17 AD patients, 12 mild cognitive impairment patients, and 62 healthy controls).

Conclusions PET scan, especially florbetapir-based radio traces in helping to diagnose early AD, is imperative to use an age-specific cutoff in MS patients to support AD diagnosis.

Highlights

- The years after the first diagnosis and progressive or non-progressive MS are crucial factors in increasing the risk of early AD.
- The florbetapir-based radio traces in helping to diagnose early AD.
- Logical to use an age-specific cutoff in MS patients for early AD diagnosis.

Keywords Neurodegenerative disease, Neuroinflammation, Neuroimaging, Dementia, Alzheimer's disease, Multiple sclerosis, Amyloid tracer, Amyloid PET scan

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Background

Multiple sclerosis (MS) is an autoimmune disease of the central nervous system (CNS). Demyelination is a hallmark pathologic feature of MS, interrupting the flow of information within the brain and between the brain and organs [1, 2]. The hallmark pathophysiology of MS is an immune response against significant proteins of the myelin sheet mainly operated through T cells and later through the release of cytokines and expression of antibodies by B cells, breakdown of the blood–brain barrier (BBB), and activation of indwelling microglia [3]. Inflammation can potentially decrease the conduction of information between neurons [4, 5]. The soluble factors released impair standard synaptic transmission and precipitate the loss of myelin sheet or even cause direct axonal damage. These and similar processes can precipitate tau accumulation as a neurofibrillary tangle and lead to Alzheimer's disease (AD) [6, 7]. Several inflammatory operations and cytokines may have a role in AD pathology. Inflammation is a standard marker of tissue destruction in any disease and may be secondary to tissue damage in AD or an immunological response marker [8]. There is increasing proof of a strong interplay between the brain's neurons and the immunological mechanisms. Fatness and systemic inflammation may intromit with immunological processes, which promote disease development [9].

Assessment of the cerebrospinal fluid for the presence and levels of amyloid-beta (Aβ) 1–40/1–42 peptides and comparing the level of total and phosphorylated tau proteins in cerebrospinal fluid [10], often in conjunction with positron emission tomography (PET) and magnetic resonance volumetric studies [11], are commonly used modalities to diagnose AD. Definitive diagnosis of AD can now be achieved through PET and via assessment of either cortical tau burden through tau-specific tracers including Fluorine-18-THK 5317, Fluorine-18-THK 5351, 18 F-flortaucipir (AV1451), and 18F-PM-PBB3 (18F-APN-1607) [12, 13, 27], or through demonstration of the presence of cortical beta-amyloid plaques through 11C-Pittsburgh compound B (PiB) or Florbetapir tracers [14, 15].

This technique plays a role in AD research. Scientists in this field can do noninvasive in vivo neuroimaging studies using PET scans in cerebral individuals with different stages of dementia [16]. According to the growing literature on the increased prevalence of AD among patients with MS and shared amyloid and tau-related pathologies, this study aimed to evaluate the advantages and disadvantages of a PET scan method for diagnosing AD in MS patients with no clinical symptoms or early-onset AD (EOAD).

Main text

Protocol and registration

Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews (**PRISMA-ScR**) checklist and explanation [17], which was developed prospectively by Peters et al. [18], was used for this study, which was revised by the Alzheimer's research team and members of Health Iran. On December 6, 2020, the Open Science Platform (OSP) (https://osf.io/xhqeg/).

Eligibility criteria

A protocol should be developed a priori, and it is essential to include the protocol information in the scoping review [18]. To ensure transparency and reduce work duplication, the protocol was registered by the OSP [19].

Inclusion criteria

Articles written in English from 2000 to 2021 that include human participants (female, male), a minimum age of 18 years, and using PET scan evaluation of AD in MS patients were evaluated in this study.

Exclusion criteria

Papers were excluded if they did not fit into the study's conceptual framework and focused on other neurodegenerative diseases or different types of dementia. Articles about AD diagnosis in patients with MS have also included letters to the editor without original data, commentaries, and editorials.

Information sources

To identify potentially relevant documents, we systematically searched international databases from 2000 to 2021: PubMed, Scopus, Cochrane Library, CINAHL, ISI Web of Science, Science Direct, PROSPERO, EMBASE, ALZFORUM, and PsycINFO. We also manually searched through the reference lists to select relevant papers. Two experienced librarians [**K.S.H, P.J**] drafted search strategies and refined them through team discussion. The final search strategy for MEDLINE is available in Additional file 1: Table S1.

The final search results were exported into EndNote, and a library technician removed duplicates. The electronic database search was supplemented by searching the Canadian Medical Protective Association website (https://www.cmpa-acpm.ca/en) and scanning-related

reviews [20]. A comprehensive literature search should be done for a scoping study, and it may include both published and difficult-to-locate or gray literature [18].

Search

The literature search strategy was peer-reviewed by (**M. KH.**) using the Peer Review of Electronic Search Strategies (**PRESS**) checklist, a set of recommendations for librarians and other information specialists to use to evaluate electronic search strategies [21], using medical subject headings (MeSH) terms (Additional file 1: Table S1).

Selection of sources of evidence

All reviewers screened the same publications, discussed the results, and revised the screening and data extraction manual before screening to increase consistency among reviewers. Four reviewers worked in pairs and evaluated the titles, abstracts, and full text of all publications identified by our searches for potentially relevant publications. We settled disagreements on study selection and data extraction by agreement and discussion with other reviewers if needed.

Data charting process

Data from eligible studies used a standardized data abstraction tool designed for this study. Two reviewers [**K.S.H., P.J.**] independently extracted data from each relevant article. Some inconsistencies were settled by consultation between the two reviewers or a third reviewer's further adjudication. REDCap, a customizable Web program based on informatics systems, was used to implement results [17].

Data items

We abstracted data on article characteristics, ID/Country, study design, population, type of tracer, and outcomes. Mean tracer standardized uptake value relative (SUVr), AD diagnosis in MS patients, and uptake of the tracers were primary outcomes. Secondary outcomes were the megabecquerel (MBq) amount of tracer and tracer side effects.

Critical appraisal of individual sources of evidence

In addition to this, a quality assessment of the selected studies was individually performed by two researchers using the modified Jadad scale for randomized controlled trial [22] Methodological Index for Non-randomized Studies (**MINORS**) tool for non-randomized interventional study [23].

A workshop on the tool was held with the team to ensure high inter-rater agreement, and two pilot tests were conducted on a random sample. Each pilot test consisted of a facilitated team meeting for feedback and discussion on discrepant items. Upon completing the pilot tests, pairs of reviewers [**K.SH., M.KH., P.J., P.P, A.M.R.R., H.K.SH, H.S, and F.R**] assessed the first included articles independently. One reviewer (P.J.) considered the remaining papers and verified them by a second reviewer [**K.SH., M.KH.**]. All inconsistencies were revised by a third reviewer [**A.M.R.R.**].

Synthesis of results

We grouped the studies by the types of behavior they analyzed and summarized the settings, populations, and study designs for each group, along with the measures used and broad findings. We identified a systematic review, counted the number of studies included in the thought that potentially met our inclusion criteria, and remarked on how many studies had been missed by our search [17].

Following the search, 508 related studies were found, and after reviewing the title and abstract of the studies, 499 studies were excluded. Our review included nine studies [24–32] (Fig. 1). The studies included; two studies that had used 18F-florbetaben [26, 31], six studies that had used [11C] PiB [24, 25, 27–29, 32], and two studies (18)F-florbetapir (18F-AV1451) [30, 32] were used for imaging. In total, 236 participants were included in this study (145 MS patients, 17 AD patients, 12 mild cognitive impairment (MCI) patients, and 62 healthy controls) (Table 1).

18F-florbetaben tracer

Forty-one patients in both studies underwent PET imaging through an 18F-florbetaben tracer [26, 31]. SUVr was higher in normal-appearing white matter (NAWM) (1.51 ± 0.12) than in damaged white matter (DWM) (1.24 ± 0.12; $P = 0.002$) [26], and also, a lower SUV ratio in NAWM and lower thalamic volume [31]. A decrease in 18F-florbetaben uptake in the damaged brain tissue was visible after imaging (Table 1).

[11C] PiB tracer

Six of the ten studies were related to the [11C] PiB PET-Scan [24, 25, 27–29, 32]. In the study by Schubert et al., 11 AD patients, 12 patients with MCI, and 20 MS patients were included [29]. In these patients, after [11C] PiB PET scan, the amount of absorption in the lateral ventricles of AD and MS was significantly reduced compared to healthy individuals. In two similar studies aimed at evaluating the [11C] PiB's uptake in white matter (WM) after imaging in patients with advanced MS, a decrease in WM uptake was observed [27, 28]. However, Kim et al. explicated that pathological relevance is obscure [24]. In another study of 16 MS

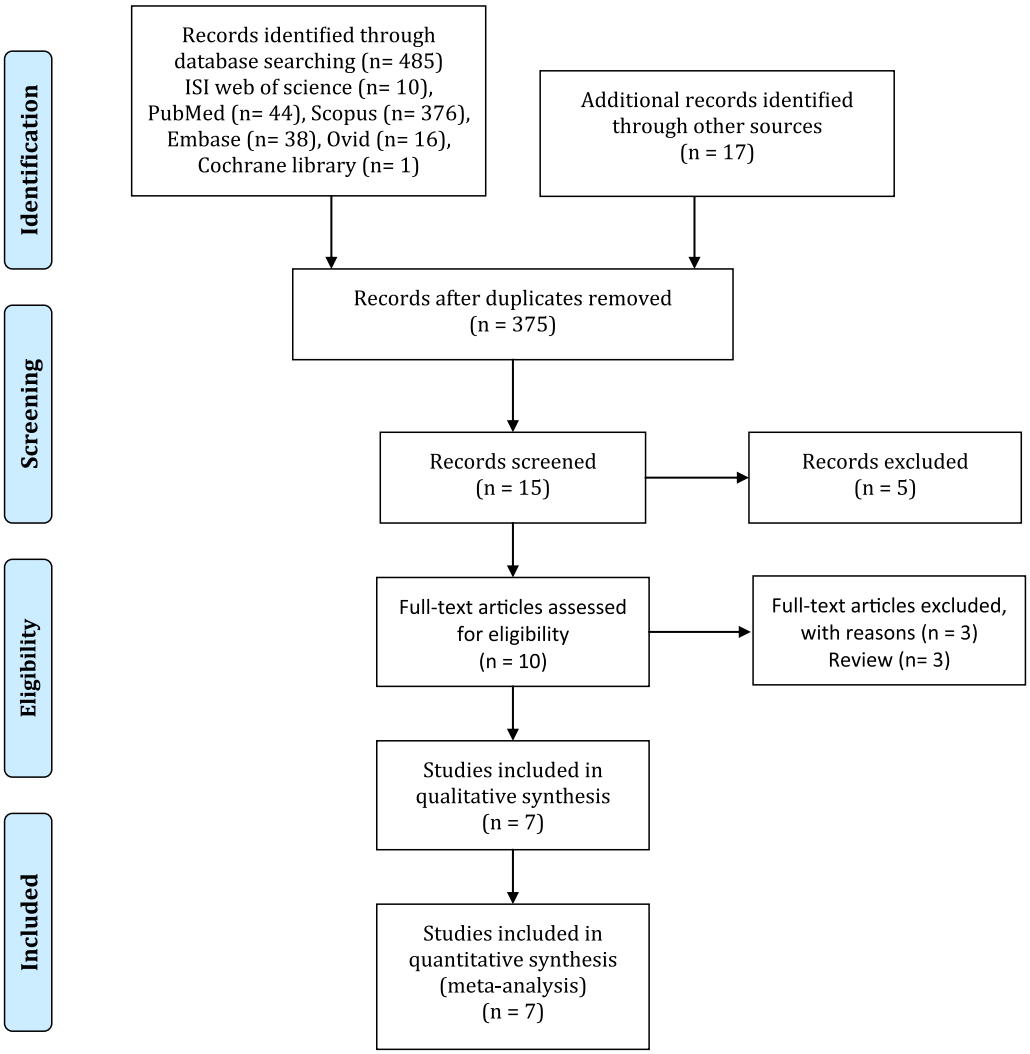

Fig. 1 Prisma flowchart diagram

patients, older patients with MS, cortical beta-amyloid deposition was decreased compared to healthy control. In contrast, tau deposition increased [32]. Reduced memory and language of MS patients significantly reduced memory, language, and dysfunction due to decreased volume of the thalamus, frontal cortex, and temporal lobe [32] (Table 1).

(18)F-florbetapir (18F-AV1451) tracer

Among three MS patients with an early cognitive impairment studied by Kolanko et al., two indicated AD through undergoing (18)F-florbetapir PET scan [30].

In another study, the frequency of elevated AD signature AV1451 SUVr was different (OR [95% CI] = 10.65 [1.10–103.35], $p = 0.04$) between patients with MS ($n = 4$, 33%) and controls ($n = 6$, 10%) [32] (Table 1).

MCI, AD, frontotemporal dementia, and dementia of Lewy body PET scan patterns

18F-florbetaben PET transaxial images of healthy control (HC), patients with Parkinson's disease (PD), dementia with Lewy bodies (DLB), MCI, AD, frontotemporal lobar degeneration (FTLD), and vascular dementia (VaD) were analyzed. AD patients show cortical 18F-florbetaben uptake and non-specific white matter uptake visible in negative scans of HC, PD, FTLD, and VaD. Sagittal and coronal amyloid PET images in AD patients demonstrate generalized increased activity within the cortical gray matter in all lobes with complete loss of gray-white

Table 1 Summary of findings

ID/country	Study design	Population	Type of tracer	Outcomes
Kolanko et al. [30]/UK	Case series	3 MS patients (A woman mid-60s diagnosed in 1994, A woman mid-70s diagnosed in 1994, A woman mid-60 diagnosed in 2000)	(18)F-Florbetapir (^{18}F-AV1451)	**Case 1**: A family history of dementia in her sister late 60s. Difficulty completing the MMSE. She had been diagnosed with MS and MRI imaging at the time had been consistent with demyelination Brain MRI showed several inflammatory demyelinating lesions API was positive **Case 2:** ACE-III score was 87/100, API was negative Brain MRI showed MS changes with little progression when compared to previous **Case 3:** ACE-III score was 87/100, API was positive MRI brain showed confluent white matter changes on MRI, but no significant change in T2 lesion load when compared to previous imaging
Zeydan et al. [32]/USA	Prospective	10 patients underwent PET imaging (12 also underwent AV1451)	[^{11}C] PiB tracer for β-amyloid and ^{18}F-AV1451 tracer for tau	Cortical β-amyloid deposition was lower in MS MS pathobiology retards the accumulation of β-amyloid but not the accumulation of tau AD signature PiB SUVr, total cortical, PiB SUVr, and the frequency of abnormal PiB SUVrs were lower in MS than controls
Vanesa Pytel et al. [31]/Spain	Prospective	29 patients underwent PET imaging	300 MBq ^{18}F-florbetaben	18F-florbetaben may be a useful biomarker in assessing myelin status in MS Increases were observed in white matter lesion burden and black hole volume but there were no significant differences in gray matter or white matter volumes No significant differences were found in MRI or PET in the level of physical disability and those who did not
Schubert et al. [29]/UK	Case series	11 AD patients (6/5 women/men; mean age: 66.5 ± 4.1 years), 12 mild cognitive impairment patients (4/8 women/men; mean age: 68.6 ± 7.9 years) and 12 matched healthy controls (5/7 women/men; mean age: 64.4 ± 6.6 years) 20 relapsing–remitting MS patients (13/7 women/men; mean age: 32.3 ± 5.6 years) and eight age- and sex-matched healthy controls (5/3 women/men; mean age: 31.6 ± 6.4 years) Female: 33	11C-PiB	Decreased 11C-PiB signal in the lateral ventricle ROIs in AD and MS patient groups compared to healthy controls Dynamic PET measures can be used to observe pathological changes in CSF dynamics Lateral ventricle 11C-PiB SUVRs were significantly lower in multiple sclerosis than in healthy controls Brain size was not found to be a significant covariate in the multiple sclerosis dataset No significant correlations were observed between gray matter 11C-PiB SUVRs and lateral ventricle. AUC35-80 in AD, mild cognitive impairment, or AD/MCI-matched control groups

Table 1 (continued)

ID/country	Study design	Population	Type of tracer	Outcomes
Zeydan et al. [28]/USA	Prospective	12 patients underwent PET imaging	292–729 MBq [^{11}C] PiB	PiB uptake was lower in areas of WM hyperintensities compared to normal-appearing WM (NAWM) in MS ($p=0.0002$) PiB uptake in the WM in late MS may be a marker No difference in global cortical PiB SUVr between patients with MS and controls in unadjusted ($p=0.35$) or WMH volume adjusted models ($p=0.49$) Using the cortical-to-cerebellar ratio cut off point of 1.42, 10 controls (17%) had a positive global cortical PiB PET scan while all MS patients were negative
Bodini et al. [27]/France	Prospective	MS ($n=20$) and healthy controls ($n=8$) (13 MS women; mean age: 32.3 years; standard deviation [SD]: 5.6), 8 healthy volunteers (5 Healthy women; mean age: 31.6 years; SD, 6.3) 19 patients who completed the study	358 ± 34 MBq [^{11}C] PiB	[11C] PiB PET allows quantification of myelin dynamics in MS Progressive reduction in [11C] PiB binding from the normal-appearing white matter to MS lesions White matter lesions were characterized by a centripetal decrease in the tracer binding at the voxel level
Matías-Guiu et al. [26]/Spain	Case series	12 patients diagnosed with MS: 5 patients had relapsing remitting MS (RRMS), 5 had secondary progressive MS (SPMS), and 2 had primary progressive MS (PPMS)	300 MBq 18F-florbetaben-18F-labeled amyloid	18F-florbetaben uptake in white matter lesions in patients with MS is lower than in NAWM no significant differences were obtained between both groups regarding age (43.60 ± 2.0 vs. 49.00 ± 6.11, $P=.07$) and total lesion volume in T2- weighted MRI (39.47 ± 20.85 vs. 30.25 ± 15.37, $P=.26$) SUVRc in NAWM was lower in MS than in the total white matter in healthy controls
Catafau et al. [25]/Germany	Review	–	[^{11}C] PiB	Amyloid PET scan as a marker of myelin is being investigated in patients with multiple sclerosis
Kim et al. [24]/Republic of Korea	Prospective	25 patients with MSA, Age 64.9 ± 9.2 years, disease duration 5.1 ± 3.0 years (MMSE) score less than 26	740 MBq [^{11}C] PiB	Cortical thinning in MSA-D was observed in areas where cortical thinning was reported in Alzheimer disease Pathological relevance is unclear

Amyloid PET Imaging (API), ACE (Addenbrooke's Cognitive Examination)-III, MBq (megabecquerel), Pittsburgh compound B (PiB), normally appearing white matter (NAWM), multiple system atrophy dementia (MSA-D), mini-mental state examination (MMSE)

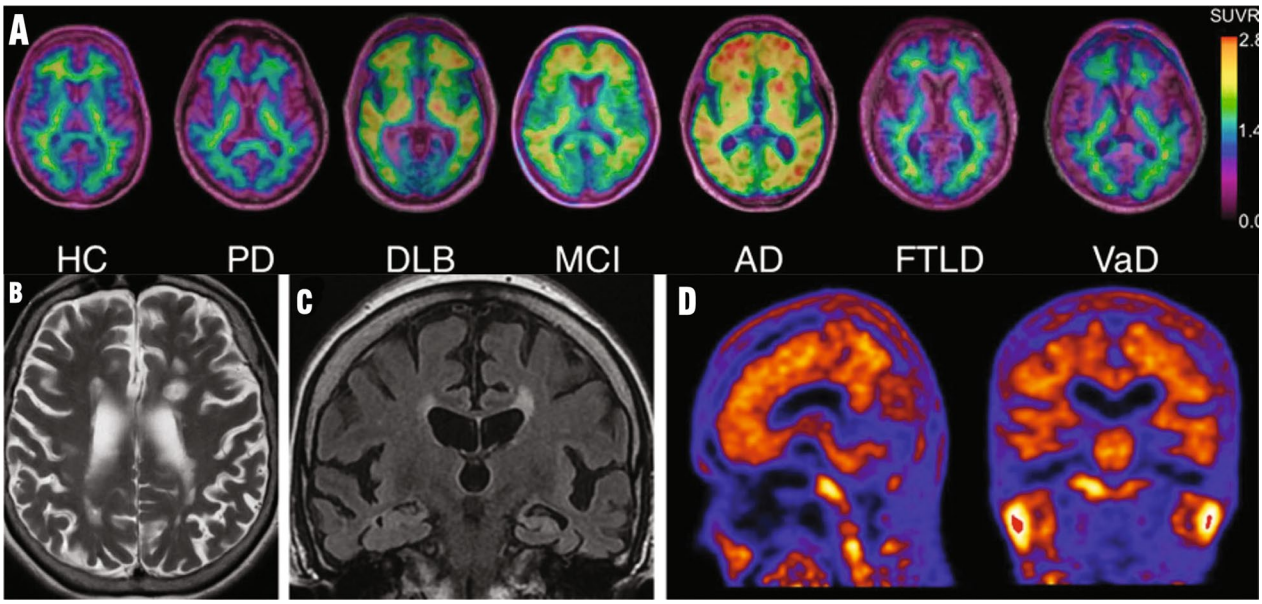

Fig. 2 **A** 18F-florbetaben PET transaxial images of healthy control (HC), patients with Parkinson's disease (PD), dementia with Lewy bodies (DLB), mild cognitive impairment (MCI), Alzheimer's disease (AD), frontotemporal lobar degeneration (FTLD), and vascular dementia (VaD). AD patients show cortical 18F-florbetaben uptake and non-specific white matter uptake visible in negative scans of HC, PD, FTLD, and VaD. All images are scaled to the same SUVR maximum. This research was initially published in JNM. Villemagne et al. B, 2011 [58]. **B** She has a family history of dementia in her sister's late 60s. Difficulty completing the MMSE. She had been diagnosed with MS, and MRI imaging had been consistent with demyelination Brain MRI showed several inflammatory demyelinating lesions. API was positive. Axial T2-weighted **C** Coronal FLAIR images through the brain showing typical MS lesions in the periventricular white matter perpendicular to the ependymal surface. Note generalized neuroparenchyma loss, with relative sparing of the temporal lobe white matter (left mesial temporal atrophy score is 2; correct mesial temporal atrophy score is 1). **D** Sagittal and coronal amyloid PET images demonstrating generalized increased activity within the cortical gray matter in all lobes with complete loss of gray-white differentiation consistent with widespread amyloid deposition. This research was initially published in J. Neurol. M Kolanko et al. 2020 [30]

differentiation consistent with widespread amyloid deposition (Fig. 2).

MS is a multifactorial demyelinating disease that is more common in women than men [33, 34]. On the other hand, immune cell function, especially microglia, causes myelin degeneration, which causes inflammation and damage to neural cells; several pathological pathways play a role in MS [2, 35]. A decrease in interleukin (IL)-10 activity as a preventive factor is an excellent cause of Th-0 dysregulation, leading to an autoimmune condition by overstimulating microglia activities [36]. In AD patients, inflammation is caused by Tau and amyloid-beta proteins [37, 38]. Overall, Inflammation in either MS and AD patients in an overlapping pathway leads to decreased cerebral blood flow (CBF), and extrinsic caspase pathway activation leads to apoptosis [4, 39] (Fig. 3). Furthermore, in the research by Campaholo et al., 51 MS patients were split into PMS and RRMS groups; as a result, the study revealed that in RRMS division, cognition and psychomotor speed were related to decreasing uptake. In another way, lower myelin content was connected to poor cognitive status [40].

Therefore, atrophic areas in the brain tissue enhance amyloid-beta and tau protein deposition probability more than in healthy individuals [41, 42]. Tau proteins have a structural role in microtubules. These proteins are separated from the microtubules following phosphorylation, disrupting the microtubules on the one hand and tangles of tau protein [43]. As though the levels of intermediate products of proteolysis of the amyloid precursor protein (APP) are decreased in patients with MS. APP has a crucially significant role in MS; APP proteolytic processing happens regarding demyelination because of the presence of myelin protein, and it also has a role in remyelination to a greater or lesser degree [44]. Following inefficient remyelination due to the function of Aβ plaques [45] and glial scars because of astrocytes [46], these plaques intensify the abnormal function of phosphorylated cyclin-dependent kinase 5 (CDK5) proteins by IL-6 and IL-18. Moreover, the effect of microglia on increasing the abnormal activity of CDK5 by IL-18 [47–50] results in the formation of hyperphosphorylated tau tangles following increases in the phosphorylation activity of phosphorylated collapsing response mediator protein 2 (pCRMP) [51, 52] (Fig. 3).

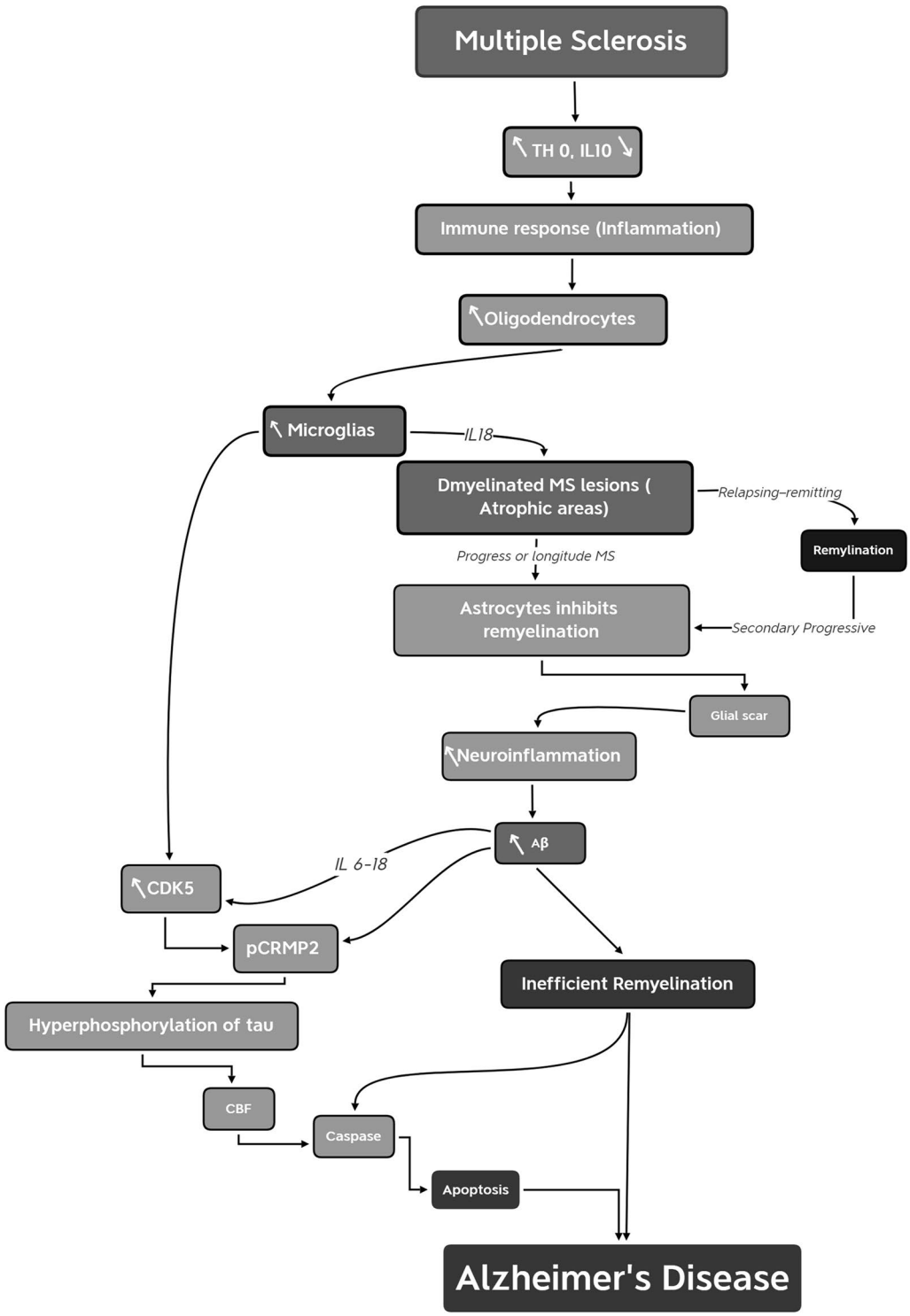

Fig. 3 Pathway between MS to neuroinflammation and AD

In that case, where MS shows itself at a younger age than AD and the possibility of increased apoptosis due to the simultaneous presence of MS and AD, a reliable diagnostic method can be helpful in the screening and prevention of AD [53]. An amyloid PET scan can recognize amyloid-beta deposits as a valuable modality in

detecting demyelination and remyelination in MS [26]. The affinity of amyloid tracers for myelin appears to be described by the β-sheet formation of both β-amyloid and myelin essential proteins [54]. In addition, this mechanism happens in other proteins, such as pathological prion protein, which is rich in β-sheet [44]. After 300 MBq of 18F-florbetaben, amyloid PET images showed decreased absorption in demyelinated areas. The pioneering research in this regard was done by Stankoff et al. [55]. In the study, Jordi et al. stated that the decrease in SUVr in the affected regions was quite apparent after MRI and PET images. It is more critical in patients with progressive MS, both primary and secondary, than in relapsing–remitting MS (RRMS) patients, showing a SUVr decrease in demyelinated areas [26, 31]. Moreover, the absorption reduction in images obtained from the amyloid PET scan, especially in primary progressive MS (PPMS) and secondary progressive MS (SPMS) compared to RRMS, could indicate a higher chance of depositing amyloid peptides in the coming years. Thus, in such cases, the 18F-florbetaben amyloid PET scan can play an essential role in diagnosing early AD in MS patients [16, 26].

N-methyl-[11C]2-(4′-methylaminophenyl)-6-hydroxybenzothiazole ([11C] PIB) due to the high bonding capability to AB plaques is useful for the detection of AD [56]. A study aimed at imaging 12 late MS patients showed decreased uptake in the white matter and frontal and temporal cortex, while uptake in other cortex areas was like healthy individuals [28]. The accurate mechanism of the physiological uptake for white matter is not well-developed, even though demyelination is the possible mechanism describing the decreased uptake in MS [54]. Similarly, Zeydan et al., AB, showed that plaque deposition decreased compared with peers in the control group by age. However, the enhancement of tau protein deposition, especially in progressive MS patients compared to the healthy control group, was significant [32]. Two studies with an almost similar design after [11C] PIB imaging reported a SUVr reduction in areas affected by MS lesions [27, 29]. In contrast, the 18F-florbetaben amyloid PET scan can detect amyloid-beta plaques in MS patients for early AD diagnosis; the white matter uptake in [11C] PiB is lower than in flora-based radiotracers such as Florbetapir and Florbetaben [15]. Similarly, [11C] PiB PET scan was shown less effective in early AD diagnosis in MS patients and more useful in identifying the cause of memory loss according to functional changes and uptake reduction in demyelinated areas [28, 32]. (18) F-florbetapir (18F-AV1451) amyloid PET scan was used by Kolanko et al. in three MS patients at least 20 years after the diagnosis; images showed a SUVr reduction and increased possibility of AD in these three patients [30]. The presence of atrophic MS lesions and a greater tendency to form accumulation in these areas automatically lead to the suspicion that the risk of AD in these patients increases due to the increased risk of AB and tau accumulation.

The amyloid brain PET imaging value is wholly based on the scan's quality and the evaluation's accuracy. This evolving modality challenges image evaluation criteria, positive and negative clinical scans, and technical imaging attention. Dependence on the Accreditation Council for Graduate Medical Education (ACGME) for safe performance of amyloid brain PET scan needs training teams that consist of physicians, expert supervision, and technician that are certified by nuclear radiology organizations and familiar with brain anatomy, metabolism, and amyloid PET tracers mechanisms [57].

Conclusions

In conclusion, MS, due to the nature of the disease and the progression of brain lesions to atrophic areas, shows that years after the first diagnosis and progressive or non-progressive MS are crucial factors in increasing the risk of early AD. With the valuable results obtained from PET scan, especially florbetapir-based radio traces, in helping to diagnose early AD, it sounds logical to use an age-specific cutoff in MS patients for early AD diagnosis.

Abbreviations

MS	Multiple sclerosis
CNS	Central nervous system
CSF	Cerebrospinal fluid
BBB	Blood–brain barrier
MRI	Magnetic resonance imaging
Aβ	Amyloid-beta
AD	Alzheimer's disease
PET	Positron emission tomography
EOFAD	Early-onset familial Alzheimer's disease
[11C] PiB	11C- Pittsburgh compound B
MeSH	Medical subject headings
SUVr	Standardized uptake value relative
PRISMA-ScR	Systematic reviews and Meta-Analyses extension for Scoping Reviews
OSP	Open Science Platform
PRESS	Peer Review of Electronic Search Strategies
MINORS	Methodological Index for Non-randomized Studies
MCI	Mild cognitive impairment
IV	Intravenously
MBq	Megabecquerel
NAWM	Normal-appearing white matter
DWM	Damaged white matter
WM	White Matter
IL	Interleukin
CDK5	Cyclin-dependent kinase 5
pCRMP	Phosphorylated collapsing response mediator protein
RRMS	Relapsing–Remitting MS
PPMS	Primary progressive MS
CBF	Cerebral blood flow

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s43055-023-00964-8.

Additional file 1: Table S1. Electronic search strategies, using medical subject headings (MeSH) terms.

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Author contributions
All authors have read and approved the manuscript.

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Availability of data and materials
All data generated or analyzed during this study are included in the supplementary material files in this article. Further inquiries can be directed to the corresponding author.

Declarations

Ethics approval and consent to participate
The paper is exempt from ethical committee approval because this is a scoping review study.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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