ORIGINAL

The effectiveness of three-dimensional (3D) PCASL MR perfusion imaging in assessing cognitive status in patients with mild cognitive impairment and Alzheimer's disease

Eficacia de la imagen de perfusión tridimensional (3D) PCASL MR para evaluar el estado cognitivo en pacientes con deterioro cognitivo leve y enfermedad de Alzheimer

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Abstract

Objective: we aimed to evaluate the relationship between CBF values obtained through PCASL MRI imaging and scores from MMSE, CDR, and CDS tests in patients diagnosed with mild cognitive impairment and Alzheimer's disease.

Materials and methods: The study encompassed four groups: Control (Group 1), Mild cognitive impairment (Group 2), Moderate cognitive impairment (Group 3), and Severe cognitive impairment (Group 4). we collected CBF values derived from Pseudo Continuous Arterial Spin Labeling Manyetik Rezonans (PCASL MRI) imaging. Additionally, for patients diagnosed with mild cognitive impairment and Alzheimer's disease, scores from MMSE, CDR, and CDS tests were meticulously documented.

Results: Significant differences were observed across the groups based on measures like MMSE, CDR, and regions of the brain such as the Frontal, Temporal, Hippocampus, PCC, Precuneus, Occipital, and Cerebellum (p<0.001 for each comparison). MMSE was significantly correlated with CDR (r= -0.736, p<0.001), Frontal (r= 0.464, p<0.001), Temporal (r= 0.325, p=0.017), Hippocampus (r= 0.509, p<0.001), PCC (r= 0.399, p=0.003), and Precuneus (r= 0.286, p=0.036). However, there was no significant correlation between MMSE and Occipital (p=0.113) or Cerebellum (p=0.535).

Conclusions: PCASL MR imaging detects neurodegenerative changes in Alzheimer's and its milder forms, supplementing neuropsychiatric evaluations like the mini-mental test. When contrasted with FDG-PET imaging, ASL MR perfusion stands out due to its non-invasive nature, absence of radiation exposure, and cost-effectiveness. Its easy applicability further underscores its prominence as a preferred diagnostic tool in assessing dementia.

Key words: Dementia, ASL MR perfusion, mini mental test score, clinic dementia rate, disability rate by mental state.

Resumen

Objetivo: Nuestro objetivo fue evaluar la relación entre los valores de CBF obtenidos mediante resonancia magnética PCASL y las puntuaciones de las pruebas MMSE, CDR y CDS en pacientes diagnosticados de deterioro cognitivo leve y enfermedad de Alzheimer.

Materiales y métodos: El estudio abarcó cuatro grupos: Control (Grupo 1), Deterioro cognitivo leve (Grupo 2), Deterioro cognitivo moderado (Grupo 3) y Deterioro cognitivo grave (Grupo 4). Recogimos valores de CBF derivados de imágenes de Pseudo Continuous Arterial Spin Labeling Manyetik Rezonans (PCASL MRI). Además, en el caso de los pacientes diagnosticados de deterioro cognitivo leve y enfermedad de Alzheimer, se documentaron meticulosamente las puntuaciones de las pruebas MMSE, CDR y CDS.

Resultados: Se observaron diferencias significativas entre los grupos en función de medidas como MMSE, CDR y regiones del cerebro como el Frontal, Temporal, Hipocampo, PCC, Precuneus, Occipital y Cerebelo (p<0,001 para cada comparación). El MMSE se correlacionó significativamente con CDR (r= -0,736, p<0,001), Frontal (r= 0,464, p<0,001), Temporal (r= 0,325, p=0,017), Hipocampo (r= 0,509, p<0,001), PCC (r= 0,399, p=0,003) y Precuneus (r= 0,286, p=0,036). Sin embargo, no hubo correlación significativa entre MMSE y Occipital (p=0,113) o Cerebelo (p=0,535).

Conclusiones: La RM PCASL detecta cambios neurodegenerativos en Alzheimer y sus formas más leves, complementando evaluaciones neuropsiquiátricas como el mini-mental test. En comparación con las imágenes FDG-PET, la perfusión ASL MR destaca por su naturaleza no invasiva, la ausencia de exposición a la radiación y su rentabilidad. Su fácil aplicabilidad subraya aún más su prominencia como herramienta diagnóstica preferida en la evaluación de la demencia.

Palabras clave: Demencia, perfusión ASL MR, puntuación del mini test mental, tasa de demencia clínica, tasa de discapacidad por estado mental.

Introduction

Dementia is a disease characterized by a decline in cognitive functions, affecting primarily memory as well as visual perception, orientation, learning and reasoning abilities, character traits, language, and higher-level motor functions. Dementia has emerged as a significant concern across public health, economic, social, and political sectors, drawing substantial and growing research investments. According to the World Alzheimer Report 2015, approximately 46.8 million individuals globally have dementia. This number is estimated to rise to 74.7 million by 2030 and further soar to 131.5 million by 2050[1-4].

In the latest guidelines published in 2011, Alzheimer's disease is presented as a spectrum. This spectrum encompasses three distinct stages: first, an early preclinical stage marked by the accumulation of amyloid plaques and neuronal and synaptic losses, but which remains symptom-free. Second, the stage of mild cognitive impairment (MCI), where based on a patient's age and educational background, there are noticeable symptoms of enhanced forgetfulness and other cognitive impairments[5]. Yet, individuals in this stage can manage daily activities without being reliant on others. Lastly, there's the final stage of dementia. Here, symptoms such as forgetfulness, difficulty in word retrieval, and challenges with visual and spatial understanding progress to the extent that individuals can no longer independently manage their daily tasks. It's noteworthy that MCI can serve as the initial cognitive indicator of Alzheimer's disease, but it might also emerge due to other neurological, vascular, metabolic, systemic, or psychiatric conditions[6].

The Mini Mental State Examination (MMSE) is a 30-point questionnaire routinely used for dementia screening, assessing cognitive functions like orientation, memory, and speech. A score of 23/24 is considered the cut-off. While quick to administer and available in multiple languages, its major drawback is its insufficiency in early Alzheimer's diagnosis and distinguishing between dementia types[7,8]. The Clinical Dementia Rating (CDR) is another scale, categorizing cognitive and functional performance in Alzheimer's and other dementias. There's also the Cognitive Disability Score (CDS) that rates the impairment level. While these neuropsychiatric tests provide qualitative data, advanced diagnostic methods such as cerebrospinal fluid analysis, PET, and MRI are now recommended. Conventional MRI primarily detects volumetric loss in medial temporal and parietal lobes for Alzheimer's. With the advent of disease-modifying treatments, methods to diagnose Alzheimer's before atrophy onset are being explored. FDG-PET, a functional imaging technique, identifies decreased glucose metabolism, a characteristic of Alzheimer's. Furthermore, imaging methods using molecular markers, like amyloid-binding PET, can identify early changes. Arterial spin labeling (ASL) MRI is a non-invasive functional imaging technique measuring cerebral blood flow. Its advantages include being non-invasive, quick, and cost-effective. Studies have shown areas of hypo-metabolism in FDG-PET coincide with hypo-perfused areas in ASL MR perfusion in Alzheimer's patients, making ASL MR perfusion a promising diagnostic tool[8,9].

In this study, we aimed to evaluate the relationship between CBF values obtained through PCASL MRI imaging and scores from MMSE, CDR, and CDS tests in patients diagnosed with mild cognitive impairment and Alzheimer's disease.

Materials and methods

Patients and design

In this retrospective analysis, our focal group encompassed patients who consulted the dementia outpatient clinic of our hospital's neurology department, primarily due to complaints of dementia. Spanning June and July 2019, these patients were subjected to MRI screenings using a 1.5 Tesla instrument as a cornerstone of our established dementia diagnostic protocol. Our comprehensive dataset incorporated a diverse age range, spanning from 50 to 86 years, and consisted of 67 individuals. The study encompassed four groups: Control (Group 1), Mild cognitive impairment (Group 2), Moderate cognitive impairment (Group 3), and Severe cognitive impairment (Group 4).

Eligibility

The inclusion parameters were meticulously defined to ensure the precision of our study. First and foremost, any patient presenting with forgetfulness at the dementia outpatient clinic was considered. They underwent a rigorous standard dementia screening process, which included not just a medical history assessment but also a holistic evaluation encompassing a physical and neurological examination. Furthermore, neuropsychiatric evaluations, laboratory tests, and MR imaging were imperative components of this screening. The subsequent diagnoses, pivotal for our study, relied heavily on established guidelines: the NINCDS-ADRDA criteria served as the backbone for diagnosing Alzheimer's disease, whereas the NIA-AA diagnostic criteria were foundational for identifying cases of mild cognitive impairment. Any patient diagnosed with either a distinct psychiatric ailment or another neurological disorder that wasn't dementia was immediately ruled out. Additionally, any cases evidencing cerebrovascular events were also omitted.

Data collection

To ensure a thorough and complete assessment, we undertook a comprehensive review of the archived follow-up files for all 67 patients from the dementia outpatient clinic. During this review, we systematically extracted several key pieces of information. This included basic demographics like age and gender, as well as specific clinical data. The clinical data encompassed results from mini-mental tests, rates of clinically diagnosed dementia, metrics related to mental state disabilities, and familial

medical histories. Furthermore, we collected CBF values derived from Pseudo Continuous Arterial Spin Labeling Manyetik Rezonans (PCASL MRI) imaging. Additionally, for patients diagnosed with mild cognitive impairment and Alzheimer's disease, scores from MMSE, CDR, and CDS tests were meticulously documented.

Ethical approval and informed consents
Approval was obtained from the Academic Council of the Department of Radiology at the University of Health Sciences with decision number 72 on 04/11/2019. Written informed consent was obtained from all individual participants and/or their gaurdians.

PCASL MR data analysis and evaluation
Raw images obtained through PCASL MR with T1-weighted gray scale were processed using GE Ready View. After automatically coloring them based on different CBF values, colored perfusion maps are generated. Through ROIs (Regions of Interest) placed in any region of the brain parenchyma, blood flow values can be measured in mL/100 gr/min. The T1 map is provided by placing the multi-TI inversion-recovery fast spin echo (IR-FSE) images, where the standard model formula "$S(t) = M0 (1-2Aexp(-tT1))$" is used. In the standard model formula, the parameter denoted by A represents the 180° pulse inversion value.

To calculate blood flow, it's necessary to calibrate the sensitivities of the images to water for each voxel. To avoid areas with the partial volume of suppressed water, the maximum neighbor algorithm is used. The C sensitivity map is created with the following formula: $C=PD/(CWM(1-exp(-TsatT1WM)))$. In this formula, PD stands for the flow-saturated proton density image intensity. CWM is the white matter tissue water concentration, which is accepted as 0.8 gm/ml. Tsat is the saturation time in the PD images and is 2 seconds. T1WM is the T1 value obtained from placing the IR-FSE images in the white matter. This calibration creates a sensitivity map named C. The value of C represents the MR signal intensity produced by one gram of water in every milliliter of brain tissue. With this C value, the brain's blood flow can be calculated using the formula: $CBF=\rho b(Sc-Sl) 2\alpha C\omega aT1aexp(-wT1a)(1-exp(-tIT1a))$. The abbreviations and values of the parameters in the formula are as follows:

- Pb represents the density of brain tissue, which is taken to be 1.05g/ml.
- α denotes the tagging efficiency, which is approximately considered to be 85%.
- W stands for Post labeling delay. For patients under 70 years of age, this is 152 ms; for those 70 and older, it is accepted as 2025 ms.
- T1a is the relaxation time of arterial blood. On the 1.5T MR device we used, this value is 1.4 seconds.
- ωa signifies the density of water in blood, which is 0.85 g/ml.
- Sl and Sc respectively represent the signal intensity in tagged images and control images.

Using the Harvard-Oxford Atlas, measurements were taken from the frontal, temporal, and occipital lobes, the hippocampus, the posterior cingulate gyrus, the precuneus, and the cerebellum through the ROIs (Regions of Interest) we placed in these areas (**Figure 1**, **2**, and **3**).

Figure 1: In the ASL MR perfusion map, ROIs placed in the hippocampus and axial T2-weighted PROPELLER sequence projections (indicated by arrows 3 and 4).
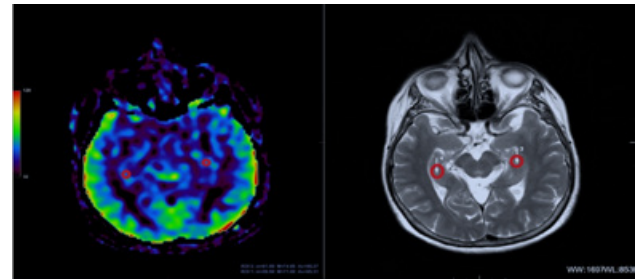

Figure 2: In the ASL MR perfusion map, ROI placed in the posterior cingulate gyrus and projection of the CUBE T1-weighted sequence (indicated by arrow 2).
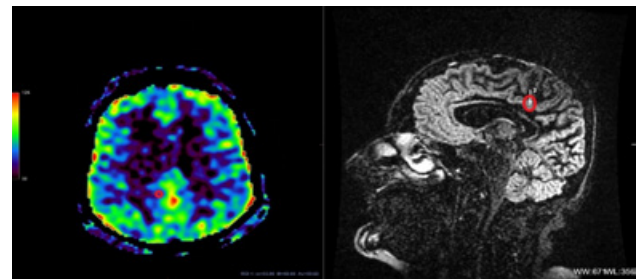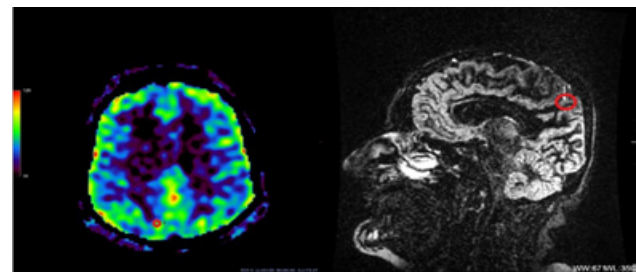

Figure 3: In the ASL MR perfusion map, ROI placed in the precuneus and projection of the CUBE T1-weighted sequence (indicated by arrow 3).

Statistical analysis
The patient information was subjected to various statistical evaluations, which included generating descriptive statistics, pinpointing frequencies, and scrutinizing factors in each category. Quantitative information was displayed as the average ± standard variation. Tests like Shapiro-Wilk and Kolmogorov-Smirnov were used to check the consistency of continuous variables. For normally distributed data, we utilized the Student's T-test and ANOVA. The Tukey post-hoc test was used for subgroups comparisons. For data that didn't follow a normal distribution, we employed non-parametric tests. The Chi-Square test was used for categorical data. The corellation between variables was determined using the Pearson test. All analyses were executed with SPSS Statistics for Windows, Version 22.0 (IBM Corp., Armonk, NY, USA). A p-value of ≤ 0.05, in a two-tailed test, was considered to indicate statistical significance.

Results

The demographic and clinical characteristics of the study participants are presented in **table I**. The mean age of the participants was 70.9 years with a standard deviation (SD) of 10.1 years. With regard to gender distribution, 59.70% (n=40) of the participants were female. The mean Mini-Mental State Examination (MMSE) score was 18.52 with a SD of 6.83, suggesting varying degrees of cognitive function among the participants. The Clinical Dementia Rating (CDR) averaged at 1.62 with an associated SD of 0.91, further emphasizing the diversity in the severity of cognitive impairment within the sample. Lastly, when inquiring about a family history of dementia or related conditions, 40.70% (n=22) of the participants reported a positive family history.

Table I: Demographic.

	n or mean	% or SD
Age (year)	70,9	10,1
Gender (F)	40	59,70%
MMSE	18,52	6,83
CDR	1,62	0,91
Family history (yes)	22	40,70%

*SD: standart deviation, MMSE: Mini-Mental State Examination, CDR: Clinical Dementia Rating.

Significant differences were observed across the groups based on measures like MMSE, CDR, and regions of the brain such as the Frontal, Temporal, Hippocampus, PCC, Precuneus, Occipital, and Cerebellum. For the MMSE, Control (Group 1) had a mean score of 27.69 (SD=1.32, N=13), which progressively decreased with severity: Group 2 had a mean of 22.33 (SD=1.91, N=18), Group 3 with 16.18 (SD=2.75, N=22), and Group 4 with 8.79 (SD=1.67, N=14) (p<0.001). Similarly, CDR scores increased with cognitive impairment severity, Group 2 at a mean of 0.81, Group 3 at 1.70, and Group 4 at 2.62 (p<0.001). When examining brain regions, starting with the frontal lobe, Group 1 had a mean value of 73.14, which decreased to 52.52 in Group 4. The hippocampus measurements for Group 1 averaged at 61.98, descending to 36.43 in Group 4. All analyzed regions presented significant differences among groups, as validated by ANOVA (p<0.001 for all parameters). The post-hoc Tukey test provided further insights into intergroup differences. Comparisons between Group 1 and Group 2 showed significant disparities for all parameters, with p-values mostly below 0.001. Group 2 and Group 3 had pronounced differences in the MMSE and CDR scores, with p-values of <0.001. A similar trend was observed when comparing Group 2 with Group 4. All paired group comparisons highlighted significant differences in many cognitive and brain regional measurements (**Table II**).

The study investigated cognitive and brain metrics differences between individuals with positive and negative family histories. For MMSE and CDR metrics, the positive history group averaged 17.22 (SD=4.92) and 1.59 (SD=0.98) respectively, compared to the negative history group's 15.68 (SD=6.12) and 1.64 (SD=0.88). Brain region comparisons, such as Frontal and Temporal, yielded similar results between groups, with no significant variations observed based on p-values. Overall, there were no major discernible differences between the two groups across the examined parameters (**Table III**).

MMSE was significantly correlated with CDR (r= -0.736, p<0.001), Frontal (r= 0.464, p<0.001), Temporal (r= 0.325, p=0.017), Hippocampus (r= 0.509, p<0.001), PCC (r= 0.399, p=0.003), and Precuneus (r= 0.286, p=0.036). However, there was no significant correlation between MMSE and Occipital (p=0.113) or Cerebellum (p=0.535) (**Table IV**).

Table II: Mean MMSE, CDR and cerebral blood flow values according to groups.

Groups		MMSE	CDR	Frontal	Temporal	Hippocampus	PCC	Precuneus	Occipital	Cerebellum
Control (Group 1)	Mean	27.69		73.14	69.11	61.98	75.88	79.87	68.37	66.09
	n	13		13	13	13	13	13	13	13
	SD	1.32		9.02	11.69	4.83	10.53	9.41	10.03	10.93
Mild cognitive impairment (Group 2)	Mean	22.33	0.81	62.96	57.30	46.48	57.37	51.08	55.14	53.61
	n	18	18	18	18	18	18	18	18	18
	SD	1.91	0.39	8.84	7.47	6.76	13.22	11.04	9.34	7.55
Moderate cognitive impairment (Group 3)	Mean	16.18	1.70	64.99	60.50	47.10	57.61	55.17	62.78	61.62
	n	22	22	22	22	22	22	22	22	22
	SD	2.75	0.80	5.27	4.53	2.46	3.70	2.20	4.43	6.97
Severe cognitive impairment (Group 4)	Mean	8.79	2.62	52.52	50.80	36.43	46.15	45.13	48.77	50.94
	n	14	13	14	14	14	14	14	14	14
	SD	1.67	0.51	11.17	8.58	7.89	9.38	11.47	11.81	10.47
p-value (ANOVA)	p	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Post-hoc Tukey test										
Group 1 vs group 2	p	<0.001	---	0.009	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Group 1 vs group 3	p	<0.001	---	0.022	0.015	<0.001	<0.001	<0.001	NS	NS
Group 1 vs group 4	p	<0.001	---	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Group 2 vs group 3	p	<0.001	<0.001	NS	NS	NS	NS	NS	0.041	0.028
Group 2 vs group 4	p	<0.001	<0.001	0.006	NS	<0.001	0.009	NS	NS	NS
Group 3 vs group 4	p	<0.001	0.002	<0.001	0.004	<0.001	0.005	0.009	<0.001	0.004

* SD: standart deviation, MMSE: Mini-Mental State Examination, CDR: Clinical Dementia Rating, PCC: Posterior Cingulate Cortex, NS: Not-significant.

Table III: Comparisons in terms of the family history.

	Positive		Negative		
	Mean	SD	Mean	SD	p-value
MMSE	17.22	4,92	15,68	6,12	0.332
CDR	1,59	0,98	1,64	0,88	0,835
Frontal	63,53	8,09	59,38	10,4	0,123
Temporal	58,53	6,98	55,81	8,08	0,206
Hippocampus	45,81	5,75	42,96	8,1	0,162
PCC	54,83	9,25	54,37	11,27	0.876
Precuneus	52,07	6,75	50,6	11,01	0.580
Occipital	57,94	9,73	55,68	10,45	0.425
Cerebellum	58,61	6,36	54,5	10,62	0.111

* SD: standart deviation, MMSE: Mini-Mental State Examination, CDR: Clinical Dementia Rating, PCC: Posterior Cingulate Cortex.

Table IV: Correlations of MMTS, CDR, frontal CBF, hippocampal CBF, PCC CBF, precuneus CBF, occipital CBF and cerebellum CBF in all dementia patients.

Correlations		MMSE	CDR	Frontal	Temporal	Hippocampus	PCC	Precuneus	Occipital	Cerebellum
MMSE	Pearson Correlation	1	-,736**	,464**	,325*	,509**	,399**	,286*	,218	,086
	Sig. (2-tailed)		,000	,000	,017	,000	,003	,036	,113	,535
	N		57	55	54	54	54	54	54	54
CDR	Pearson Correlation		1	-,292*	-,155	-,356**	-,336*	-,206	-,194	,030
	Sig. (2-tailed)			,032	,269	,009	,014	,139	,165	,829
	N			54	53	53	53	53	53	53
Frontal	Pearson Correlation			1	,687**	,569**	,639**	,570**	,629**	,453**
	Sig. (2-tailed)				,000	,000	,000	,000	,000	,001
	N				54	54	54	54	54	54
Temporal	Pearson Correlation				1	,532**	,618**	,581**	,748**	,589**
	Sig. (2-tailed)					,000	,000	,000	,000	,000
	N					54	54	54	54	54
Hippocampus	Pearson Correlation					1	,767**	,726**	,512**	,556**
	Sig. (2-tailed)						,000	,000	,000	,000
	N						54	54	54	54
PCC	Pearson Correlation						1	,889**	,670**	,536**
	Sig. (2-tailed)							,000	,000	,000
	N							54	54	54
Precuneus	Pearson Correlation							1	,651**	,608**
	Sig. (2-tailed)								,000	,000
	N								54	54
Occipital	Pearson Correlation								1	,713**
	Sig. (2-tailed)									,000
	N									54
Cerebellum	Pearson Correlation									1
	Sig. (2-tailed)									
	N									

* SD: standart deviation, MMSE: Mini-Mental State Examination, CDR: Clinical Dementia Rating, PCC: Posterior Cingulate Cortex.

Discussion

In this study, we found that PCASL MR perfusion imaging is a highly successful method in determining the severity of dementia, especially in distinguishing severe dementia. Until today, previous studies have used various ASL techniques (pulsed and continuous) to examine CBF in MCI (Mild Cognitive Impairment) and Alzheimer's patients. All of them have demonstrated decreased CBF patterns, mainly located in the posterior cingulate cortex, precuneus, and bilateral parietal areas[10-16]. Only two of these studies directly compared the CBF of Alzheimer's patients, MCI patients, and control cases, and both used voxel analysis on 1.5-T non-whole brain data. Johnson and colleagues used relative CBF measurements to compare AH and MCI patients with a control group, identifying regions of relative hypoperfusion in patients diagnosed with AH in the bilateral posterior cingulate cortex, precuneus, and right inferior parietal lobe[12]. An overlapping but weaker pattern was found in MCI patients. Dai et al. found decreased CBF in the posterior cingulate cortex, precuneus, and inferior parietal cortex in AH and MCI patients, and the areas of hypoperfusion in AH were more extensive than those seen in MCI[15,17].

In our study, similarly, when patients with subjective complaints in the control group were compared with patients with mild cognitive impairment, moderate dementia, and severe dementia, CBF measurements from all brain regions were found to be higher in the control group. Again, the most significant decrease in

CBF values compared to the control group in all patient groups was observed in the precuneus, PCC, and hippocampus, consistent with the literature. However, when we compared the groups of severe dementia, moderate dementia, and mild cognitive impairment with each other, the lowest CBF values for all brain regions were present in the severe dementia group. Patients with moderate dementia and mild cognitive impairment had similar CBF values.

In the study by Binnewijzend and colleagues, we see that CBF values, adjusted for partial volume, are lower in all brain regions except the cerebellum in the patient group with Alzheimer's disease compared to the control group (1). Similar findings were obtained in our study, and the results were found to be consistent with this study. The positive correlation observed between hippocampal and PCC blood flow values, and between PCC and precuneus blood flow values in all patients except the control group, indicates the relationship between these neurofunctionally affected regions in dementia patients. This underscores that our study is in alignment with the literature.

When CDR was compared separately with CBF values from seven different regions in the brain for every patient group, including the control group, no significant correlation was found between the variables in any of the patient groups. However, when all dementia patients were combined into a single group for analysis, a negative correlation was identified between hippocampal and PCC CBF values and CDR. The significant emergence of the correlation in the study was attributed to the increased sample size resulting from the combination of patient groups. This correlation reflects the relationship between neurocognitive level and CBF. Additionally, When the CBF values, clinical dementia rates and mini-mental test scores of those with a positive family history were compared with those with a negative family history, no significant difference was detected.

This study had several limitations. Firstly, our sample size was small. Secondly, the study was conducted using a 1.5T MRI machine. A higher magnetic field increases the signal-to-noise ratio. In comparison to 3T, 1.5T yields images with a lower signal-to-noise ratio. Thus, the fact that the study was performed using a 1.5T MRI machine is considered one of the limitations. Another limiting factor was that our workstation could not process raw images through various specialized programs to obtain partial volume corrections, remove tissues outside the brain, and perform tissue segmentation. The partial volume effect wasn't precisely and accurately calculated due to relatively low image resolution and limited tissue sampling. Another constraint was that the control group consisted of patients with subjective complaints rather than healthy individuals. We didn't conduct multiple scans at different delay times for each patient group to obtain the most appropriate labeling. Instead, images were acquired by adopting the optimal PLD parameter values recommended by Grade et al.'s study: 1525 ms for patients under 70 years old and 2025 ms for those over 70 [180]. We didn't adjust for potential factors that could affect brain perfusion, such as diabetes, smoking, and caffeine consumption shortly before the MRI scan.

Conclusions

CBF values calculated in PCASL MR imaging reveal functional changes in the brain due to neurodegeneration in Alzheimer's disease and its milder clinical presentations, providing quantitative data that assist neuropsychiatric scores such as the mini-mental test, clinical dementia rating, and disability score according to mental state. In comparison to FDG-PET imaging, the absence of radiation exposure and non-invasive features, as well as its easy applicability and cost-effectiveness, place ASL MR perfusion in a more advantageous position, emphasizing its usefulness as a diagnostic tool in dementia evaluation.

Conflict of interest
No

References

1. Binnewijzend MAA, et al. Cerebral blood flow measured with 3D pseudocontinuous arterial spin-labeling MR imaging in Alzheimer disease and mild cognitive impairment: a marker for disease severity. Radiology. 2013;267(1):221-30.

2. Swerdlow RH. Pathogenesis of Alzheimer's disease. Clin Interv Aging. 2007;2(3):347-59.

3. Albert MS, et al. The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement J Alzheimers Assoc. 2011;7(3):270-9.

4. Petersen RC, Lopez O, Armstrong MJ,et al. Practice guideline update summary: Mild cognitive impairment: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology. Neurology. 2018 Jan 16;90(3):126-35.

5. Braak H, Braak E. Staging of Alzheimer-related cortical destruction. Int Psychogeriatr. 1997;9(Suppl 1):257-261.

6. Jagust WJ, et al. Relationships between biomarkers in aging and dementia. Neurology. 2009;73(15):1193-9.

7. Frisoni GB, Fox NC, Jack CR, Scheltens P, Thompson PM. The clinical use of structural MRI in Alzheimer disease. Nat Rev Neurol. 2010;6(2):67-77.

8. Arevalo-Rodriguez I, et al. Mini-Mental State Examination (MMSE) for the detection of Alzheimer's disease and other dementias in people with mild cognitive impairment (MCI). Cochrane Database Syst Rev. 2015;(3):CD010783.

9. Ishii K. PET approaches for diagnosis of dementia. AJNR Am J Neuroradiol. 2014;35(11):2030-8.

10. Alsop DC, Detre JA, Grossman M. Assessment of cerebral blood flow in Alzheimer's disease by spin-labeled magnetic resonance imaging. Ann Neurol. 2000;47(1):93-100.

11. Chao LL, et al. Patterns of Cerebral Hypoperfusion in Amnestic and Dysexecutive MCI. Alzheimer Dis Assoc Disord. 2009;23(3):245-252.

12. Johnson NA, et al. Pattern of cerebral hypoperfusion in Alzheimer disease and mild cognitive impairment measured with arterial spin-labeling MR imaging: initial experience. Radiology. 2005;234(3):851-9.

13. Xu G, et al. Reliability and precision of pseudo-continuous arterial spin labeling perfusion MRI on 3.0 T and comparison with 15O-water PET in elderly subjects at risk for Alzheimer's disease. NMR Biomed. 2010;23(3):286-93.

14. Yoshiura T, Hiwatashi A, Noguchi T, Yamashita K, Ohyagi Y, Monji A, Nagao E, Kamano H, Togao O, Honda H. Arterial spin labelling at 3-T MR imaging for detection of individuals with Alzheimer's disease. Eur Radiol. 2009 Dec;19(12):2819-25.

15. Dai W, Lopez OL, Carmichael OT, Becker JT, Kuller LH, Gach HM. Mild cognitive impairment and alzheimer disease: patterns of altered cerebral blood flow at MR imaging. Radiology. 2009;250(3):856-66.

16. Alexopoulos P, et al. Perfusion abnormalities in mild cognitive impairment and mild dementia in Alzheimer's disease measured by pulsed arterial spin labeling MRI. Eur Arch Psychiatry Clin Neurosci. 2012;262(1):69-77.

17. Iranmanesh, H. Genome-scale reconstruction and systems analysis of brain microglial cells. Academic Journal of Health Sciences: Medicina Balear, 2022;37(1), 156-60.