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Original Research Article

Asymmetric Cerebral Blood Flow in Patients with Mild Cognitive Impairment: Possible Relationship to Further Cognitive Deterioration

Åke Edman[a] Lars Edenbrandt[b, c] Johan Fredén-Lindqvist[b]
Magnus Nilsson[b] Anders Wallin[a]

[a]Institute of Neuroscience and Physiology and [b]Department of Molecular and Clinical Medicine, Clinical Physiology, Sahlgrenska University Hospital, Sahlgrenska Academy, University of Gothenburg, Gothenburg, and [c]Department of Clinical Sciences, Lund University, Malmö, Sweden

Key Words
Cerebral blood flow · Cognitive decline · Mild cognitive impairment · Progressive dementia · SPECT

Abstract
Aim: To explore patterns of cerebral blood flow in patients with mild cognitive impairment (MCI), who (1) eventually deteriorate into overt dementia, with no particular focus on the type of dementia, or (2) do not appear to further deteriorate in their cognitive functions. ***Methods:*** Thirty-seven MCI patients, with or without vascular pathology, were studied prospectively. The patients underwent ^{99m}Tc-HMPAO SPECT analysis at baseline. Possible clinical conversion into dementia within a 2-year period was assessed. ***Results:*** Nineteen patients had progressive MCI (PMCI), while 18 patients were considered clinically stable (SMCI). PMCI patients had more often abnormally low cerebral blood flow in at least one of the frontal, temporal, parietal or occipital lobes compared to SMCI patients (12/19 vs. 5/18; $p = 0.049$). At least one of the temporal regions was found to be abnormal in 9 PMCI patients in contrast to only 1 SMCI patient ($p = 0.008$). More specifically, blood flow in the medial portion of the left temporal region was abnormal in 8 PMCI patients, a pattern seen in 1 SMCI patient only ($p = 0.019$). ***Conclusion:*** The results suggest that blood flow reductions particularly in the left medial temporal region indicate an elevated risk of further cognitive decline in MCI patients.

Åke Edman
Vuxenpsykiatriska mottagningen
Träslövsvägen 25B, SE–43243 Varberg (Sweden)
Tel. +46 340 482 411, E-Mail ake.edman@neuro.gu.se

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Introduction

Mild cognitive impairment (MCI) represents a borderline condition between normal cognition and dementia. Subjects with MCI are at a higher risk of converting into overt dementia than subjects with normal cognition [1, 2]. Since Alzheimer's disease (AD) is considered to be the most common form of dementia [3], prodromal AD is probably the most frequent single MCI disorder. However, MCI is most likely a heterogeneous condition, i.e. an MCI patient who further deteriorates in his/her cognitions into overt dementia may develop one of many possible dementia disorders [4]. It would, therefore, seem relevant to study the eventual cognitive outcome in MCI patients with focus not only on AD, the presence or absence of which has been the endpoint in the vast majority of studies on MCI progression.

It is probable that several dementia treatments with curative intention will be available in the fairly near future [5, 6]. In this context, there is reason to believe that the patient would benefit from treatment intervention already in the early phases of progressive cognitive disorders. It is important, therefore, to acquire knowledge on markers for progressive degenerative and vascular pathogenesis already in the incipient stages of dementia. Conversely, it is equally important to acquire knowledge on markers for non-progressive cognitive disorder.

Magnetic resonance imaging studies have revealed an association between hippocampal atrophy and later development into overt dementia [7], whereby left hippocampal atrophy may be a particularly sensitive predictor [8]. Furthermore, it has been demonstrated that the cerebrospinal fluid biomarker levels of τ, phosphorylated τ and amyloid β_{1-42} ($A\beta_{42}$) are altered already at the MCI stages in patients who will, eventually, suffer from AD [9–11].

Results from prospective FDG-PET studies suggest that subnormal metabolic rates of glucose consumption in temporoparietal and hippocampal regions in MCI patients [12] predict future conversion into overt AD. In a prospective study on cerebral blood flow imaging with SPECT, blood flow reductions in several brain regions, including the parietal and temporal lobes and posterior cingulate, appeared to indicate future conversion from MCI into AD [13].

The aim of the present prospective study was to further explore possible patterns of cerebral blood flow reduction in a clinical population of MCI patients, who (1) eventually deteriorate into overt dementia, or (2) do not appear to further deteriorate in their cognitive functions. Patients with vascular pathology were not excluded, except for patients with a history of cerebral stroke. Separate quantification of left and right medial temporal lobe blood flow was included in the protocol. Blood flow was measured by way of hexamethyl propylene amine oxime (HMPAO)-SPECT, a technique which is relatively simple and widespread in medical care in comparison with the PET technique. Results from blood flow studies that utilize SPECT, instead of PET (which enables a higher-power resolution), may therefore be of more immediate importance in medical care.

Materials and Methods

Study Population

Thirty-seven patients with MCI were studied. They were part of the Gothenburg MCI Study, which is a longitudinal study on MCI and mild dementia performed at the Department of Neuropsychiatry, Göteborg University, Sweden, and approved by the Ethics Committee of the University (reference: L 091-99). The patients had given their informed consent. Those included in the present study were the first consecutive subjects who (1) underwent SPECT analysis at baseline; (2) were assessed for MCI with a baseline score of 3 on the Global Deterioration Scale (GDS), and (3) did not have a history of major stroke.

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Table 1. Demographic data and MMSE scores at baseline

		PMCI	SMCI
Age, years	Mean	66.9	66.5
	SD	6.7	7.4
	Range	51–78	54–77
Gender	Males	8	11
	Females	11	7
MMSE	Mean	27.3	28.1
	SD	1.5	1.7
	Range	23–29	24–30

The categorization of patients with regard to MCI and (unspecified) dementia was based on anamnestic data and checklists for cognitive assessment: (1) Stepwise Comparative Status Analysis (STEP) [14], variables 13–20 (memory disturbance, disorientation, reduced abstract thinking, visuospatial disturbance, poverty of language, sensory aphasia, visual agnosia, and apraxia); (2) IFlex, which is a short form of the Executive Interview [15] (number-letter task, word fluency, anomalous sentence repetition, interference task, Luria's hand sequences, and counting task); (3) Mini-Mental State Examination (MMSE) [16], and (4) Clinical Dementia Rating (CDR) [17]. The CDR assessment was based on information from both the subject and an informant. For inclusion, subjective and objective (by an informant) verifications of a progressive cognitive impairment for >6 months were required. In addition, a positive outcome on STEP, IFlex, MMSE or CDR was required. Subjects with >2 positive outcomes on STEP or a score <25 on the MMSE were considered to fulfill criteria for dementia and were, consequently, not included in the present study [18]. The above algorithm is congruent with recent diagnostic recommendations [2]. Based on the scores, patients were classified according to the GDS where 3 equals MCI and 4 mild dementia [19].

Nineteen patients converted clinically into dementia within 2 years (progressive MCI, PMCI), while 18 patients were considered clinically stable during the same time period (stable MCI, SMCI). Conversion into the dementia syndrome was assessed according to the algorithm outlined above. The patients who converted to dementia suffered from the following clinical disorders: AD (n = 7) according to the NINCDS-ADRDA criteria [20], subcortical vascular dementia, SVD, (n = 3) according to the criteria of Erkinjuntti et al. [21], mixed AD/(subcortical) vascular dementia, MD (n = 7), progressive non-fluent aphasia (n = 1) according to the criteria of Neary et al. [22], and dementia non-ultra descriptum where no particular dementia disorder was possible to identify clinically (n = 1). Baseline demographics are presented in table 1. No statistical difference was found between the PMCI and SMCI groups with regard to age, gender, or baseline performance on MMSE.

SPECT analysis was not included in any diagnostic procedure.

SPECT Imaging

All patients underwent ^{99m}Tc-HMPAO SPECT at baseline. About 1,000 MBq of ^{99m}Tc-HMPAO was administered intravenously after a 15- to 20-min period of resting in a quiet and dimly lit room. The subjects had their eyes closed during the resting period and the injection. Imaging acquisitions were performed with a 3-headed Picker Irix γ-camera (Philips Medical Systems Inc., Hamburg, Germany) with high-resolution collimators about 45 min after the injection. A 128 × 128 pixel matrix was used and 90 projections were registered with an acquisition time of 45 s each. The image reconstruction was performed with filtered back-projection and a Butterworth filter (cutoff 0.5 cycles/cm) on a Picker Odyssey FX820

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System (Philips Medical Systems Inc). Attenuation was modeled to be uniform (linear attenuation coefficient = 0.11 cm^{-1}) inside the skull volume. No scatter subtraction was performed. The resulting transaxial slice images were then transferred to a software for semiquantitative analysis (EXINI brain™; EXINI diagnostics AB, Lund, Sweden). The software comprises a 3-dimensional method based on a brain-shaped model and the active shape algorithm. The method defines the surface shape of the brain and then projects the maximum counts 0–1.5 cm deep for designated surface points. These surface projection values are divided into cortical regions representing the different lobes and presented relative to the whole cortex, cerebellum, or cerebellar maximum. The whole brain and the cerebellum are the most common reference regions used, but they do not always represent the best choice. In patients with reduced blood flow in these regions, quantitative data may be inaccurate. As an alternative reference region, the maximum value of the cerebellum was added to the quantification method.

The mean time between baseline clinical assessment and SPECT imaging was 140 (SD 77) days in the PMCI group and 105 (SD 81) days in the SMCI group; the difference is statistically not significant (p = 0.187).

Image Analysis

The brain surface is automatically outlined 3-dimensionally by the program. The cortical blood flow is calculated in relation to the blood flow of one of three reference regions (cortex – the whole cortical part of the brain; $cerebellum_{tot}$ – the cortical part of cerebellum, and $cerebellum_{max}$ – the maximum intensity of cerebellum). The relative blood flow values are compared to the corresponding values of a normal database and z-values are calculated. The normal group consisted of 30 healthy volunteers, 20 females and 10 males, with a mean age of 74.4 years (SD 7.8; range 64–98). Mean z-values are calculated of each of 10 brain regions (frontal lobe dx/sin/med, temporal lobe dx/sin/med-dx/med-sin), parietal lobe (dx/sin) and the whole occipital lobe. The differences in blood flow between the left and right sides are also calculated for the frontal, temporal and parietal lobes, and compared to the corresponding normal values.

Statistical Analyses

Relationships between categorical variables were tested using Fisher's exact test and relationships between continuous variables were tested using Student's t test.

Results

The number of patients with abnormal baseline findings in the parietal, temporal, frontal, and occipital lobes are presented in table 2. Patients with PMCI had more frequently abnormal findings in the cerebral blood flow in at least 1 of the 4 regions compared to the SMCI group (12/19 vs. 5/18; p = 0.049), using the $cerebellum_{max}$ normalization method. The 12 cases included 4 of the 7 AD patients and 7 of the 10 dementia patients with obvious cerebrovascular disease (SVD + MD; non-significant difference between the patient groups). The 17 patients with reduced blood flow had a mean MMSE of 27.8 compared to a mean MMSE of 27.6 in the remaining patients without reduced blood flow. This difference was not significant, i.e. a relationship between cognitive performance and reduced blood flow could not be found. At least one of the temporal regions was abnormal in 9 of the PMCI patients, but only in 1 SMCI patient using the same normalization method (p = 0.008). The 9 cases included 2 of the 7 AD patients and 6 of the 10 SVD + MD patients (non-significant difference between the patient groups). More specifically, the blood flow in the medial portion of the

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Table 2. Number of patients with significantly decreased blood flow in 10 brain regions [frontal lobe (right, left, medial), temporal lobe (right, left, right medial, left medial), parietal lobe (right, left) and occipital lobe]

Normalization	Cortex		$Cerebellum_{tot}$		$Cerebellum_{max}$	
	PMCI (n = 19)	SMCI (n = 18)	PMCI (n = 19)	SMCI (n = 18)	PMCI (n = 19)	SMCI (n = 18)
Frontal dx	0	0	1	1	1	0
Frontal sin	3	2	4	2	2	2
Frontal med	0	0	1	0	1	2
Temporal dx	0	0	1	1	1	1
Temporal sin	1	1	2	2	1	1
Temporal med dx	3	2	5	3	5	1
Temporal med sin	5	3	8	2	8*	1*
Parietal dx	7	5	7	2	6	4
Parietal sin	8	9	9	4	6	4
Occipital	1	0	1	2	0	2
Total	16	13	12	8	12**	5**

Cortex, $cerebellum_{tot}$, $cerebellum_{max}$: reference regions for blood flow calculation (see Image Analysis above). * p = 0.019, ** p = 0.049.

left temporal region was abnormally low in 8 PMCI patients, a pattern seen only in 1 SMCI patient (p = 0.019). There were no significant differences in blood flow between the patient groups in the frontal, parietal, and occipital lobes.

Measurements of relative blood flow as a continuous variable are presented in table 3. No differences in mean z-values (standard deviations from the mean of a normal database) between PMCI and SMCI were found in the parietal, temporal, frontal, or occipital lobes.

In addition, a significant side difference in cerebral blood flow was found in 11 patients, 7 PMCI (3 MD, 2 AD, 1 SVD, and 1 progressive non-fluent aphasia) and 4 SMCI (table 4). In all cases, the cerebral blood flow was lower on the left compared to the right side.

Discussion

The present study demonstrated that MCI patients who deteriorated into overt dementia within the following 2-year period exhibited more often abnormal cerebral blood flow at baseline than did patients with SMCI. The most distinct finding was a blood flow reduction in the medial portion of the left temporal region in 8 of 19 PMCI patients, a pattern seen in 1 of 18 SMCI patients only (using the $cerebellum_{max}$ method).

We did not find any significant differences in the measurements of relative blood flow as a continuous variable between the PMCI and SMCI groups. The analysis was made separately for the frontal, temporal, parietal and occipital lobes. Abnormal findings in at least one of these regions were, however, more frequent in the PMCI group compared to the SMCI group. This finding indicates that the PMCI patients are a heterogeneous group and that abnormalities in their cerebral blood flow can appear in different locations rather than as a homogeneous gradual decrease in blood flow in a specific location.

It is fairly well established that blood flow reductions in parietal brain regions, medial temporal regions, precuneus and posterior cingulate gyrus predict cognitive decline [13, 23–25] and the development of clinically manifest AD in MCI patients [26]. Also, the pres-

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Table 3. Blood flow in relation to a normal database presented in z-values (standard deviations from mean)

Normalization	Cortex		$Cerebellum_{tot}$		$Cerebellum_{max}$	
	PMCI (n = 19)	SMCI (n = 18)	PMCI (n = 19)	SMCI (n = 18)	PMCI (n = 19)	SMCI (n = 18)
Frontal dx	0.68+1.48	0.32+0.88	–0.24+1.29	–0.27+0.89	–0.35+0.95	–0.27+0.92
Frontal sin	–0.78+1.17	–0.76+0.70	–0.93+1.10	–0.78+0.81	–0.92+0.86	–0.70+0.87
Frontal med	–0.33+0.76	–0.34+0.93	–0.63+0.89	–0.54+0.87	–0.71+0.82	–0.55+1.06
Temporal dx	1.21+1.26	1.31+0.85	0.16+1.39	0.39+1.21	–0.02+1.04	0.26+1.13
Temporal sin	0.03+1.52	0.12+0.91	–0.58+1.35	–0.36+1.12	–0.59+1.13	–0.33+1.04
Temporal med dx	–0.99+0.85	–0.79+1.03	–1.20+1.01	–0.94+0.85	–1.18+1.01	–0.88+0.83
Temporal med sin	–1.55+1.80	–1.31+0.73	–1.60+1.51	–1.32+0.60	–1.52+1.49	–1.21+0.74
Parietal dx	–1.77+0.95	–1.44+0.97	–1.68+0.92	–1.35+0.86	–1.51+0.68	–1.17+0.83
Parietal sin	–1.97+1.08	–1.60+1.03	–1.82+1.03	–1.46+0.84	–1.63+0.84	–1.27+0.86
Occipital	–0.43+1.17	–0.70+0.63	–0.86+0.72	–0.89+0.83	–0.80+0.61	–0.75+0.87

No differences in mean values between PMCI and SMCI were statistically significant (t test).

Table 4. Number of patients with significant side differences in cerebral blood flow with regard to frontal, temporal, and parietal lobes, respectively

Lobes	PMCI (n = 19)		SMCI (n = 18)		p value	
	L < R	R < L	L < R	R < L	PMCI vs. SMCI	L < R vs. R < L
Frontal	7	0	4	0	NS	0.003
Temporal	4	0	0	0	NS	NS
Parietal	1	0	0	0	NS	NS
Total	7	0	4	0	NS	0.003

Total: number of patients with significant side difference in at least 1 region. L < R and R < L = Significantly lower cerebral blood flow in the left region than in the right region and vice versa.

ence of AD-typical cortical atrophy on MRI appears to predict future cognitive deterioration in patients with MCI [27]. With regard to the possible importance of asymmetrical blood flow patterns, presence of left-sided reduction in the posterior cingulate gyrus has been reported in a SPECT study on PMCI [28]. Also, a SPECT study by Nobili et al. [29] demonstrated reduced blood flow in the left hippocampus in amnestic MCI. Conversely, another SPECT study demonstrated right-sided parietal and hippocampal blood flow reductions in PMCI [30]. One study employing functional MRI demonstrated *increased* blood flow in the left hippocampus in MCI, a finding which was interpreted as a possible (transient) compensatory mechanism in incipient AD [31]. In summary, the present study and the literature provide results which appear to be contradictory with regard to the existence and possible importance of asymmetrical cerebral blood flow in MCI.

There was no significant difference in frontal lobe blood flow between PMCI and SMCI patients in the present study. This finding is in contrast to findings in SPECT studies by Huang et al. [23, 24], in which blood flow in frontal brain regions of PMCI patients was increased compared with SMCI patients and healthy controls. In a recent MR/SPECT study on amnestic MCI [32], a *negative* correlation was found between entorhinal/hippocampal volumes and blood flow in frontal brain regions – and a *positive* correlation between entorhinal/

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hippocampal volumes and blood flow in the posterior cingulate gyrus, whereby the latter finding possibly reflects deafferentation. Taken together, the above results in the literature indicate the presence of transient compensatory frontal functions in subgroups of MCI patients prior to conversion into overt dementia.

In conclusion, the results of the present study support the view that blood flow reductions in the left medial temporal region indicate an elevated risk of further cognitive decline in MCI patients. Unfortunately, the SPECT literature in the field of MCI prognostics reports the use of varying progression markers and varying brain regions of interest. Furthermore, inclusion criteria may vary. In the present study, for instance, information on left/right handedness was not included in the protocol. These circumstances make comparisons between studies somewhat difficult [33].

Finally, a note on the choice of the imaging method is worth being mentioned. FDG-PET, one alternative imaging technique, appears to be a more distinct marker of cognitive decline compared to SPECT [33]. The FDG-PET technique appears to have the ability even to predict future MCI in clinically healthy persons [34]. Furthermore, Pittsburgh Compound-B PET appears to be a promising method for early identification of emerging AD [35, 36]. However, the SPECT technique is in most countries more often available than PET. Data from prediction studies based on SPECT and robust assessments of cognitive status, such as GDS, would, therefore, possibly be of more immediate importance in general health care.

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Disclosure Statement

Lars Edenbrandt is employed and shareholder in EXINI diagnostics AB, which owns the software EXINI brain described in this paper.

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