

Impact of Vascular Risk Factors and Diseases on Cognition in Persons with Mild Cognitive Impairment

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Key Words

Amnesic mild cognitive impairment • Vascular burden •
Vascular risk factors • Executive impairment

Abstract

Background/Aim: To investigate the impact of vascular burden (assessed by the number of vascular risk factors and diseases) on the cognition of persons with amnesic mild cognitive impairment (aMCI). **Methods:** This study included 145 participants; 68 meeting criteria for amnesic single-domain or multiple-domain MCI and 77 matched controls. Four cognitive domains were assessed: executive functions, processing speed, episodic memory and general cognitive functioning. **Results:** A larger vascular burden among aMCI is correlated with lower performance in the executive domain. In addition, persons with aMCI with high vascular burden were more frequently of the multiple domain subtype, whereas persons with no vascular burden were more frequently of the single domain subtype. **Conclusion:** Our findings suggest that the combined effect of multiple vascular risk factors and diseases increases the amount of executive impairment in persons with aMCI. Vascular burden may play an important role in the heterogeneity of aMCI by impairing cognitive functions other than memory.

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Introduction

Previous studies have shown that vascular risk factors and diseases unmask [1] and accelerate cognitive decline in older persons [2–4]; moreover, they are also associated with future development of Alzheimer's disease (AD) [4] and vascular dementia [5–7]. There is evidence that among the different cognitive domains, executive functions [8–11] and cognitive speed [2, 8, 12, 13] are most likely to be altered by the presence of vascular risk factors and diseases in healthy older adults. Conversely, vascular burden has a milder impact on episodic memory [7, 12, 13], language [7] or verbal intelligence [12]. Thus, vascular risk factors and diseases are hypothesized to disturb cognitive functions that rely on the frontal networks. One important question to address is whether vascular risk factors and diseases contribute to the cognitive profile of older persons with mild cognitive impairment (MCI). Individuals with MCI have mild cognitive deficits and are at high risk of developing dementia [14]. Persons with MCI are characterized by marked memory deficits and show brain atrophy in the mediotemporal areas of the brain [15]. Whether vascular risk factors and diseases influence memory deficits in MCI is unclear. In turn, it is recognized that MCI is a heterogeneous entity at the cognitive level, and increasing evidence points to early ex-

Table 1. Clinical and neuropsychological scores in controls and MCI participants

Measures	Controls (n = 77)	MCI (n = 68)
Age, years	70.40 ± 9.55	70.65 ± 8.66
Sex		
Female	58	39
Male	19	29
Education	14.01 ± 3.41	14.51 ± 4.44
MMSE (/30)	28.99 ± 0.95	27.53 ± 2.20**
MDRS (/144)	140.56 ± 3.05	135.62 ± 6.57**
Key figure copy (score)	32.72 ± 3.39	30.28 ± 3.78**
BEM immediate recall (/12)	9.03 ± 1.81	6.63 ± 2.28**
BEM delayed recall (/12)	8.68 ± 1.78	5.9 ± 2.67**
RL/RI-16 free recall trial (/16)	11.90 ± 2.07	9.19 ± 3.52**
RL/RI-16 delayed free recall (/16)	12.40 ± 2.18	9.81 ± 3.66**
Stroop color reading (time)	18.18 ± 5.49	20.24 ± 6.27*
Stroop color naming (time)	13.54 ± 3.75	14.97 ± 3.76*
Stroop color interference (time)	29.84 ± 9.63	34.63 ± 13.55*
Brown-Peterson interference	31.06 ± 4.55	25.47 ± 6.96**

MMSE = Mini-Mental Status Examination. MDRS = Mattis Dementia Rating Scale. T tests significant at * $p < 0.05$, ** $p < 0.01$.

ecutive impairment in this population [16]. It is, however, unclear whether part of this heterogeneity is related to the presence of vascular risk factors and diseases in a subset of the persons with MCI that show executive as well as memory impairment.

The present study has three goals. First, to examine whether vascular burden (assessed by the presence and number of vascular risk factors and diseases) in persons with MCI is associated with lower performance in executive functions and cognitive speed as is the case in healthy older adults, or whether their memory is also sensitive to the presence of a vascular burden. Second, since the presence of multiple vascular risk factors and diseases has been suggested to have a cumulative effect on cognitive deficits [7, 17–19], the effect of having a single vascular risk factor or a single vascular disease in contrast to multiple vascular risk factors and diseases was also assessed. Finally, this study aimed to assess if vascular burden could account for the cognitive heterogeneity of MCI. Indeed, recent classifications [20] have been proposed that distinguish MCI individuals with isolated memory deficit (single-domain amnesic MCI, aMCI), from MCI persons with memory deficits plus deficits in other cognitive domains, most often executive (multiple-domain aMCI). Therefore, given that vascular burden is associated with executive and speed deficits in healthy older adults, we assessed whether MCI persons with a higher vascular burden were encountered more frequently in the category

of multiple-domain aMCI (memory plus executive and/or speed deficits) rather than in the category of single-domain aMCI.

Methods

Participants

This study included a total of 145 participants, including 68 persons with aMCI and 77 healthy elderly controls. The demographic, clinical and neuropsychological characteristics of all participants are presented in table 1. aMCI participants were recruited from memory disorders clinics belonging to tertiary referral centers in Montreal. Clinical criteria for the diagnosis of aMCI included (a) memory complaint, preferably corroborated by an informant, (b) performance at least 1.5 standard deviations below age and education normative values on memory tests, (c) possible impairment in other cognitive domains, (d) essentially preserved activities of daily living, and (e) no dementia [20]. Their cognitive impairment had no significant repercussions on functional independence. This was assessed for each individual patient by completing the SMAF scale (le Système de Mesure de l'Autonomie Fonctionnelle) [21]. Individuals with aMCI had a medical, neurological, neuropsychological and clinical assessment to support diagnosis and exclude other causes for the cognitive deficits. In addition, the majority of aMCI individuals had a brain scan, which is more readily available than a brain MRI in our community, as part of their clinical evaluation. This was used to exclude severe brain damages (i.e. stroke or brain tumor) as a cause for their mild cognitive impairment. All the scans were interpreted clinically and deemed to be within normal limits including those showing the presence of age-consistent atrophy or

age-consistent white matter changes. Controls were recruited from a pool of volunteers living in the community in Montreal. They underwent the same clinical and neuropsychological evaluation and were only included in the study if they performed within norms on cognitive tests (scores that did not reach the cutoff of 1.5 SD below normative values). In both groups, persons having had a general anesthesia in the last 6 months, history of neurological diseases or events (i.e. stroke, Parkinson's disease, epilepsy, brain anoxia), psychiatric disorder (schizophrenia, major depression, alcoholism) or traumatic brain injury were excluded from this study. Presence of other chronic diseases was not a reason for exclusion. All participants were francophone persons living in the Montreal area, and most of them were of Western European descent, primarily French. The group was thus ethnically homogeneous.

When subsequently following up our patients, we found that 57.1% of those with more than one vascular risk factor showed a significant cognitive decline or converted to dementia, whereas 37.0% MCI with zero or one risk factor or disease showed a significant cognitive decline or converted to dementia. This difference did not reach significance ($\chi^2 = 0.17$).

Cognitive Assessment

All participants were tested on a range of cognitive tests. Performances on these tests were used to derive four cognitive composite scores: [1] executive functions [2], processing speed [3], episodic memory and [4] general cognitive functioning. Composite scores were used to minimize the likelihood of type 1 error arising from multiple comparisons and to reduce inter-test noise. First, the control group was separated by median split to obtain a group of younger-age controls (age ≤ 70) and older-age controls (age > 70). This ensured that composite scores of MCI participants were derived relative to a group of age-appropriate controls. For each participant, a composite score was then determined by averaging his/her Z score measures that targeted each cognitive domain (see below). Z scores were calculated individually by subtracting the mean of the age-matched reference group from the raw score obtained by the participant, and by dividing this difference by the standard deviation of the age-matched reference group.

The composite score for executive functions was obtained by averaging Z scores on the time taken in the interference condition of the Victoria Stroop paradigm [22] and the Z scores on the interference condition of an adapted version of the Brown-Peterson Procedure task [23]. In the Stroop task, color names are printed in an incongruent ink color (i.e. the word 'green' is printed in yellow ink) and participants have to report the color of the ink as fast as possible. The Brown-Peterson procedure requires participants to maintain short series of letters over varied delays (0, 10, 20 or 30 s) while completing an interfering counting task. In the present analysis, the Stroop task's score was reversed because higher scores represent poorer performance which is not the case in the Brown-Peterson Procedure task.

The composite score for processing speed was obtained by averaging Z scores on the time taken in the reading and in the naming condition of the Stroop task. These conditions were selected to reflect processing speed because they are simple speed tasks and as such are likely to be independent of executive functions, contrary to the more complex speed tasks (i.e. Digit Symbol) that were used in other reports.

The composite score for episodic memory was obtained by averaging trace decay score from the RL/RI word recall task [24] and trace decay score from the BEM story recall task [25]. Because some types of memory processes are caused by executive impairments, we selected memory scores that reflected consolidation, a process less dependent on executive functions, and strongly impaired in AD [26]. The RL/RI word recall task is an episodic memory task that measures free and cued recall while controlling for the encoding of information. In the BEM story recall task participants are asked to recall a short story. Trace decay scores were obtained by subtracting delayed free recall from immediate free recall and then dividing the difference by immediate free recall in both tasks [(immediate-delay)/immediate].

The general cognitive functioning composite score was obtained by averaging Z scores on the Mini-Mental Status Examination [27] and Z scores on the Mattis Dementia Rating Scale [28], two measures of cognitive status widely used to screen for dementia.

Participants with MCI were classified as multiple-domain MCI (n = 17) if they had an executive and/or a processing speed composite score that was less than -1.5 (that is they performed at least 1.5 standard deviations below the reference control group) in addition to their clinical memory deficit. They were classified as single-domain MCI (n = 51) if they performed within normal limit (above the -1.5 cutoff) on both of these composite scores and thus only showed clinical memory deficit.

Index of Vascular Burden

Vascular burden was measured by recording risk factors (hypertension, hypotension, dyslipidemia and diabetes mellitus) and diseases (carotid stenosis, history of coronary artery disease, transient cerebral ischemia and cardiac arrhythmia) clinically reported or recorded in the individual charts of patients by their treating physician. Those vascular risk factors and diseases were selected from the vascular risk factor index [29] as a function of their high prevalence in healthy older adults, and ease for reporting and analysis. This resulted in some of the lifestyle risk factors to be excluded. For example, smoking, which is a well-recognized vascular risk factor, was not considered because quantity and duration are often not mentioned in the patients' charts. Selected factors were then added up in each patient to obtain a vascular burden index. This strategy was taken based on Song et al. [29] that posits that the number of vascular risk factors determines the rate of vascular cognitive impairment and death, irrespective of their nature. The presence of vascular risk factors and diseases was assessed as patients were enrolled in the study by relying on information in clinical records, information provided by participants during the medical interview and information provided by proxies. This information was available for all participants included in the study.

Statistical Analysis

T tests were used to determine if aMCI and controls differed on sociodemographic characteristics and on the index of vascular burden. Kendall's correlations computed between the index of vascular burden and the four cognitive composite scores were used to assess if vascular burden was associated with cognitive performances. Nonparametric correlations were performed because the distribution of the vascular burden was not normal and because the distributions of the cognitive composite scores were

Table 2. Nonparametric correlations between the index of vascular burden and the four cognitive composite scores in aMCI and controls

	Executive functions	Processing speed	Episodic memory	General cognitive functioning
aMCI	-0.24*	0.15	0.11	-0.12
Controls	-0.05	-0.03	-0.02	-0.08

* p < 0.05.

Table 3. Mean executive composite score in aMCI with no vascular factor, aMCI with one vascular factor and aMCI with more than one vascular factor

	Number of vascular factors		
	0	1	>1
Executive function composite score	-0.51	-0.86	-1.72**, *

** p < 0.01, different from the group with no vascular factor;
* p < 0.05, different from the group with one vascular factor.

characterized by a large number of tied ranks [30]. Moreover, a one-way ANOVA was conducted that included the between-subjects factor vascular burden [three levels: zero vascular risk factor or disease (n = 34), one vascular risk factor or one disease (n = 20) and more than one vascular risk factor or disease (n = 14)] to assess if the combined effect of several vascular risk factors and diseases amplified the cognitive deficit associated with vascular burden in aMCI. To avoid multiple comparisons, this analysis was done only on the variables that were significantly correlated with vascular burden. Mean comparisons were then performed with Bonferroni post-hoc tests with a 95% confidence level. Finally, a χ^2 analysis was used to determine if aMCI persons with a high vascular burden were more frequent in the category of multiple-domain aMCI than in the category of single-domain aMCI.

Results

Sociodemographic Data

The control group was comparable to the aMCI group for age, $t(147) = -0.16$, $p = 0.87$, two tailed, and education $t(143) = -0.77$, $p = 0.44$, two tailed. The control group had a mean age of 70.40 years (SD = 9.55) and a mean number of years of education of 14.01 (SD = 3.41). The aMCI group had a mean age of 70.65 years (SD = 8.66) and a mean

number of years of education of 14.51 years (SD = 4.44). We also assess if groups differed on sex using a χ^2 test. The control group had significantly more women (58 women, 19 men) than the aMCI group (39 women, 29 men), $\chi^2(2) = 5.27$, $p < 0.05$.

Index of Vascular Burden

There was no group difference on the vascular burden score [$t(147) = -0.30$, $p = 0.77$, two tailed] the aMCI group had a mean score of 0.85 (SD = 1.02) and the control group had a mean score of 0.90 (SD = 1.01).

Correlation Analysis between Cognitive Composite Scores and Vascular Burden

Table 2 shows the results of the correlational analyses between the index of vascular burden and the four cognitive domains. There was a significant negative correlation in aMCI between the vascular burden and the executive composite score, $\tau = -0.23$, $p < 0.05$, two tailed. The correlation indicates that larger burden indices were associated with lower scores on executive function in aMCI. There was no other significant correlation in aMCI. There was no significant correlation in the control group. These results were not changed when separating groups as a function of age or education. Data are thus presented here for the entire group.

Additive Effect of Multiple Vascular Risk Factors and Diseases on Executive Function in aMCI

Table 3 shows the performance of executive score of aMCI as a function of vascular burden considered as a categorical variable (aMCI with zero vascular risk factor or disease, aMCI with one vascular risk factor or disease and aMCI with more than one vascular risk factor or disease). The ANOVA indicated a main vascular burden effect, $F(2, 68) = 5.89$, $p < 0.01$. Post-hoc analyses indicated that there was no significant difference on executive composite scores among aMCI with zero vascular risk factor or disease and those with one vascular risk factor or disease, $p = 1$. However, aMCI with more than one vascular risk factor or disease demonstrated poorer executive composite score than those with either zero, $p < 0.01$ or one vascular risk factor or disease, $p < 0.05$. These results were not changed when separating groups as a function of age or education. Data are thus presented here for the entire group.

MCI Subtype as a Function of Vascular Burden

Table 4 shows a difference in the distribution of the classification of aMCI as a function of the load of their

vascular burden, $\chi^2(2) = 10.89, p < 0.01$. aMCI with a high vascular burden were more frequently classified as multiple-domain aMCI, whereas those with no vascular burden were more frequently classified as single-domain aMCI.

Discussion

The aim of this study was to investigate the impact of vascular burden on cognitive heterogeneity in aMCI. We first sought to determine whether vascular burden impairs the same cognitive domains in aMCI as in healthy older adults or whether it amplifies the memory deficits that are characteristic of aMCI. Our results indicate that vascular burden is related to executive dysfunctions in aMCI similar to what has been repeatedly reported in healthy older adults [8, 11]. In this study, vascular burden was not associated with processing speed, episodic memory or overall cognitive functioning. The lack of relationship between processing speed and vascular burden is different from what has been reported by some studies in healthy older adults [2, 12, 13]. Inconsistencies between studies finding a relation and those failing to find one might arise from the nature of the tasks used to measure processing speed. Indeed, results similar to ours were observed when using simple psychomotor speed tasks [13]. In contrast, studies reporting a relation between speed and vascular burden have typically used complex cognitive speed tasks (i.e. Digit Symbol). Thus, vascular burden may be associated with impairment in complex speed tasks that are highly demanding for the frontal lobe (i.e. the Digit Symbol test), but not with simpler speed tasks [31].

We also sought to determine the relationship between the number of vascular risk factors and diseases and cognitive deficits. The results of this study suggest that multiple vascular risk factors and diseases increase the amount of executive impairment in a nonlinear fashion. This is consistent with a threshold effect that has been postulated for cognitive impairment arising from vascular injury to the brain [32]. This is also consistent with recent data linking hypertension and executive deficits in MCI [33]. Moreover, this is in line with the notion of frailty, whereby it is the cumulative effect of deficits (i.e. vascular diseases) that has a more profound effect on the vulnerability of a person to morbidity and mortality [34, 35]. These findings underscore the importance of optimally managing multiple vascular risk factors and diseases.

Table 4. Classification of aMCI as a function of vascular burden

	Number of vascular factors		
	0	1	>1
Single domain	30 (58.8%)	15 (29.4%)	6 (11.8%)
Multiple domain	4 (23.5%)	5 (29.4%)	8 (47.1%)

Pearson χ^2 is significant at $p < 0.01$.

The last goal of this study was to assess whether vascular burden plays a significant role in the clinical classification of aMCI. In the present study, persons with aMCI with a high vascular burden were more frequently of the multiple domain subtype, whereas persons with no vascular burden were more frequently of the single domain subtype. This important finding supports a role for the vascular burden on the cognitive heterogeneity of aMCI. Subjects with aMCI and a heavy vascular burden tend to have more extensive cognitive deficits. Individuals with more extensive cognitive deficits might be at higher risk for functional impairment or conversion to overt dementia on follow-up [36], and this needs to be taken into consideration in their management.

The presence of an association between vascular burden in aMCI and their pattern of cognitive deficits has a number of implications. First, aMCI is a heterogeneous entity at the cognitive level. Indeed, whereas a significant proportion of persons with aMCI have isolated memory deficit (or single-domain aMCI), a large portion have deficits in other cognitive domains, mostly executive, in addition to memory deficits (or multiple-domain aMCI). In a recent review that focuses on the relationship between vascular risk factors and MCI, Panza et al. [37] proposed that vascular risk factors may play an important role in the cognitive heterogeneity of MCI. Our findings indicate that vascular risk factors and diseases contribute to amnesic multiple-domain MCI by impairing executive function in those with memory deficits. In addition, findings from this study suggest that vascular burden affects cognition in a pattern that is slightly different from what is expected in AD. Instead of increasing memory deficits that are characteristic of early AD, vascular burden impairs executive functions which are more typically associated with subcortical vascular dementia [38–39]. Thus, rather than impairing the mediotemporal brain network involved in episodic memory and associated with early brain changes in AD, vascular burden seems to impair

the frontal-subcortical network, which is thought to underlie the cognitive deficits in subcortical vascular dementia [40]. This may underscore the fact that aMCI may be a precursor to a number of different disorders including AD and vascular dementia. However, executive deficits have been reported in early AD [41, 42], and it is also possible that vascular burden precipitates the expression of those deficits that would otherwise occur later in the evolution of the disease. Hence, by increasing the level of pathological brain damage, vascular burden may reduce the brain reserve and thus increase and/or accelerate the expression of executive impairment in early AD. Further research will be needed to assess the prognosis and progression of aMCI with a heavy vascular burden.

Finally, those results further emphasize the importance of treating vascular risk factors and diseases in MCI and AD when possible [43–45]. They suggest that by controlling for vascular risk factors and diseases, it might be possible to prevent or attenuate the executive deficit among aMCI.

Limitations

There were fewer participants that had multiple vascular risk factors and diseases than participants that had zero or one vascular risk factor or disease. This is probably due to a recruitment bias as most of our patients were recruited from memory clinics. Of note is the fact that there were no clear outliers in this group. Nevertheless, this study needs to be replicated by using recruitment strategies that promote the inclusion of a larger number of participants that have multiple vascular risk factors and diseases. The absence of systematic brain imaging and reliance on nonoptimal brain imaging assessment (i.e. CT scan rather than MRI) is another limitation, but the goal of this study was to focus on vascular risk factors and diseases as clinically measured and not on brain im-

aging. Furthermore, clinical brain imaging was available in most participants to exclude those with major brain diseases, including stroke. It is believed that simple clinical assessment used in this study has a better potential of widespread use than sophisticated imaging techniques. Another potential limitation is our use of a binary assessment of the vascular risk factors and diseases (i.e. presence/absence) rather than using a continuous scale (e.g. blood pressure, blood glucose level). Of note however, the use of a continuous scale is not necessarily amenable to all of the factors assessed here and it is unclear whether a one unit change is equivalent across those measures. Our study does not allow assessing the relative contribution of different risk factors because most of them were insufficiently represented to allow such a fine grain analysis, though it might be interesting for future studies to assess whether different factors have different impact on cognition. Finally, this study needs to be replicated with larger sample size and when possible, in a community-based sample in order to generalize our findings to the overall population. Note, however, that the advantage of our design is that the population is representative of the clinical population consulting physicians for memory complaints. In addition, relying on a relatively smaller sample size facilitated the use of a fairly extensive neuropsychological battery.

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