Vascular risk factors and white matter hyperintensities in patients with amnestic mild cognitive impairment


Background – Subjects affected by aMCI are considered at high risk for AD. Nevertheless, the role of both vascular risk factors and WMH is matter of debate. Patients and Methods – We enrolled consecutively 21 aMCI subjects according to Petersen Criteria; the study included routine screening for dementia, neuropsychological evaluation and brain MRI. Six vascular risk factors were assessed and WMH was quantified by means of a semiautomatic lesion-detection program. Results – Conversion to AD, according to NINCDS-ADRDA criteria, was 47.6%. Converters tended to be more affected by the most of vascular risk factors while no difference was noted in WMH. The best predictors of conversion to AD were scores obtained at several neuropsychological examination. Conclusion – Our results show that criteria for aMCI identify subjects with a high risk to develop AD. WMH doesn’t seem to have a role in progression from aMCI to AD, while some vascular risk factors seem to promote it.

Background

Mild cognitive impairment (MCI) has been recognized as a condition interposed between normal ageing and dementia (1–3). Several clinical subtypes of MCI do exist. The main distinction is between MCI with memory deficit, referred to as amnestic MCI (aMCI), and MCI without memory deficit, referred to as non-amnestic MCI (naMCI) (4). Though few prospective studies are available, elderly people with aMCI are considered at high risk for Alzheimer’s disease (AD) (5, 6). The clinical course of aMCI is, however, heterogeneous (7), probably owing to the interplay of genetic, physiological, environmental and pathological features (8). Although the contribution of vascular risk factors in the onset of AD is widely documented (9, 10), their role in the progression from aMCI to AD is a matter of debate (11, 12).

White matter hyperintensities (WMH), as expression of vascular damage, are known to be very common in aged people (13) and can, according to some authors, affect cognitive functions (14). However, the relationship between WMH and both AD (15, 16) and the progression from aMCI to AD is still unclear (17, 18).

The main aim of this study was to estimate the role of various vascular risk factors and WMH in the progression from aMCI to AD. The secondary aim was to evaluate the occurrence of AD in a continuous series of patients with aMCI.

Methods

Subjects

We selected 21 subjects (mean ± SD age, 72.6 ± 5 years, range 61–81 years; 8 males and 13 females) affected by aMCI according to Petersen Criteria (4) from a cohort of newly referred consecutive patients (n = 325) from the memory clinic of the Department of Neurological Sciences of the University of Rome ‘La Sapienza’, between January 2001 and January 2003.
Fifteen subjects were not included because poor memory test performance was judged to be related to vascular cognitive impairment or to a history of cerebral vascular events, alcohol abuse, psychiatric illness, depression, medical disease or intake of medications that might affect brain function, such as typical and atypical neuroleptics and benzodiazepines.

All subjects who were demented according to Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) were excluded (n = 209), as well as subjects who performed normally at neuropsychological evaluation (n = 35) and subjects who presented a naMCI (n = 45).

All the subjects who were invited to participate gave their informed consent to the study and no dropout was observed during the follow-up. aMCI subjects selected had a Clinical Dementia Rating score of 0.5 and a Hamilton Depression Scale score < 17. The mean Mini-Mental State Examination (MMSE) score ±SD was 27.1 ± 2.8 (range 24–30). None of the aMCI was administered anti-dementia drugs.

At baseline, the study protocol included a physical and neurological examination, a blood sample for complete cell count, complete blood chemistry analysis, erythrocyte sedimentation rate, serum glucose, blood urea nitrogen, creatinine, aspartate aminotransferase (AST) and alanine aminotransferase (ALT), urinalysis, folate, vitamin B12, thyroid hormones, veneral disease research laboratory (VDRL), a neuropsychological evaluation and brain magnetic resonance imaging (MRI).

A follow-up was planned every year. The mean duration of follow-up was 2.5 years (range 2–3). At follow-up, all aMCI subjects were re-evaluated for the diagnosis of probable AD according to National Institute of Neurological and Communicative Disease and Stroke (NINCDS)-Alzheimer’s disease and related disorders association (ADRDA) criteria (19). The neuropsychological examination was repeated if clinical evaluation and MMSE score suggested a worsening of cognitive deficit.

Assessment of vascular risk factors

The presence/absence of six vascular risk factors was assessed from interviews with both the subjects and informants: (i) arterial hypertension: history of blood pressure measurements greater than 160/95 mmHg or antihypertensive medication intake; (ii) hypercholesterolaemia: serum cholesterol level over 220 mg/dl or statin intake; (iii) hypertriglyceridaemia: serum triglycerides level over 140 mg/dl; (iv) diabetes mellitus: plasma glucose level over 110 mg/dl or anti-diabetic drug intake; (v) heart disease: previous myocardial infarction or electrocardiographic evidence of atrial fibrillation; (vi) smoking: more than five cigarettes per day for at least 5 years; not smoking: less than five cigarettes per day or stopped smoking for 10 years.

Neuropsychological tests

Cognitive performance was evaluated by means of a battery of neuropsychological tests widely used in the clinical setting; the raw scores for each test were adjusted for age and education according to the Italian normative data.

The tests were selected to investigate the following areas of cognition: selective attention (Attentional matrices) (20), episodic memory (Story Recall test) (21), non-verbal logical reasoning and problem-solving ability (Raven’s Coloured Progressive Matrices) (22), word generation by phonological and semantic cues [Phonological (F-P-L) and semantic (animals) Verbal Fluency test] (23), auditory comprehension of complex sentences (Token test) (20), spatial abilities and constructional praxis (Copying Drawings) (20). Subjects presenting isolated deficit in episodic memory were considered to be affected by aMCI.

Brain magnetic resonance imaging

Patients underwent a brain MRI [1.5 T; Philips Gyroscan, Philips Medical Systems, Eindhoven, the Netherlands] examination. The following sequences were performed: proton density, T2-weighted (TR: 3000 ms, TE: 10/110 ms), T1-weighted (TR: 350 ms, TE: 14 ms) and T2-weighted fluid-attenuated inversion recovery (FLAIR) (TR: 6000 ms, TE: 100 ms). All sequences had a matrix of 256*256 mm and axial orientation; 20 transverse 6 mm-thick sections, gap 0.6 mm, were obtained.

The total volume of the vascular lesions, defined as WMH, was evaluated on T2-FLAIR sequences using a semiautomatic lesion-detection program (Dispimage; D. Plummer, London, UK), running on a free-standing computer workstation (Sun Sparc 10; Sun Microsystem, Mountain View, CA, USA). Measurements were obtained by means of a mouse-controlled cursor by clicking on the perimeter of the lesion on the computer display. The program outlines the lesion by following the contour of isointensity from the initial edge point, thus defining the lesion as a region in which the signal intensity is locally higher than the signal intensity at the initial edge position. This
sometimes yields poor results because other structures adjacent to the lesion, such as grey matter, may be equally bright, leading to a contour that moves away from the lesion’s perimeter. Whenever this happened, the lesions were manually outlined by an operator. Each outline was stored on a computer disk before the total lesion volume was automatically calculated. Images were measured by an operator who was blinded to the clinical data. None of the patients showed any abnormalities at MRI other than WMH or small incidental lacunar lesions (< 5 mm).

Statistical analysis

Statistical analyses were performed by means of nonparametric tests (Mann–Whitney test, Spearman’s correlation) as well as the chi-squared test with Fisher’s correction.

The odds ratio and relative 95% confidence interval were calculated (univariate logistic regression). \( P < 0.05 \) was considered statistically significant. All analyses were performed using the Statistical Package for the Social Sciences (SPSS, Version 13.0; SPSS Inc., Chicago, IL, USA).

Results

Table 1 shows clinical and socio-demographic characteristics of our population. By the end of the follow-up, 10 subjects (47.6%) had converted to AD according to NINCDS-ADRDA criteria, while the aMCI diagnosis was confirmed in the remaining 11 subjects (52.4%); none recovered from memory deficit (Fig. 1) or converted to other kinds of dementia.

Total WMH volume tended to correlate with age (\( r = 0.41, P = 0.06; \) Spearman’s correlation) and no significant correlation was found with any vascular risk factors. No differences in age, gender, memory deficit duration or education were found between converters and non-converters; moreover, both groups had the same vascular load (Mann–Whitney test).

Differences in vascular risk factors between converters and non-converters are shown in Table 2. Subjects who developed AD tended to be affected more by hypertension, diabetes, hypertriglyceridaemia and heart disease, though less by smoking. The only vascular risk factor which reached statistical significance was hypercholesterolaemia, which was higher in non-converters (OR: 0.042; 95% CI: 0.004–0.485). Subjects were divided into two groups, according to the number of

Table 1 Clinical and socio-demographic characteristics of 21 subjects affected by aMCI

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>72.6 ± 4.9</td>
</tr>
<tr>
<td>Symptom onset (months)</td>
<td>30.9 ± 18.4</td>
</tr>
<tr>
<td>Education (years)</td>
<td>10.1 ± 5.1</td>
</tr>
<tr>
<td>Vascular load (mm³)</td>
<td>1710.9 ± 1737.4</td>
</tr>
<tr>
<td>MMSE baseline</td>
<td>26.9 ± 3.2</td>
</tr>
<tr>
<td>Token Test</td>
<td>31.2 ± 1.6 (29)*</td>
</tr>
<tr>
<td>Raven’s Matrices</td>
<td>28.7 ± 3.9 (18)*</td>
</tr>
<tr>
<td>Story Recall Test</td>
<td>5.6 ± 2.1 (8)*</td>
</tr>
<tr>
<td>Semantic Fluency Test</td>
<td>15.6 ± 4.7 (9.5)*</td>
</tr>
<tr>
<td>Phonological Fluency Test</td>
<td>31.3 ± 9.3 (16)*</td>
</tr>
<tr>
<td>Attentional Matrices</td>
<td>49.7 ± 12.9 (30)*</td>
</tr>
<tr>
<td>Copying Drawings</td>
<td>12.5 ± 1.3 (8)*</td>
</tr>
<tr>
<td>Sex (male/female)</td>
<td>8/13</td>
</tr>
<tr>
<td>Hypertension (yes/no)</td>
<td>6/4</td>
</tr>
<tr>
<td>Diabetes (yes/no)</td>
<td>2/19</td>
</tr>
<tr>
<td>Hypercholesterolaemia (yes/no)</td>
<td>9/12</td>
</tr>
<tr>
<td>Hypertriglyceridaemia (yes/no)</td>
<td>3/18</td>
</tr>
<tr>
<td>Heart disease (yes/no)</td>
<td>3/18</td>
</tr>
<tr>
<td>Smoking (yes/no)</td>
<td>11/10</td>
</tr>
</tbody>
</table>

aMCI, amnestic mild cognitive impairment.  
*Cut-off values of normal range (numeric variables expressed as mean ± standard deviation; qualitative variables expressed as ratio).

Table 2 Rating of relative risk of conversion to AD with regard to vascular risk factors in 21 aMCI subjects

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Converters</th>
<th>Non-converters</th>
<th>( \chi^2 )</th>
<th>( P )</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension (yes/no)</td>
<td>6/4</td>
<td>4/7</td>
<td>–</td>
<td>2.6</td>
<td>(0.4–15.3)</td>
</tr>
<tr>
<td>Diabetes (yes/no)</td>
<td>2/8</td>
<td>0/11</td>
<td>–</td>
<td>0.1</td>
<td>–</td>
</tr>
<tr>
<td>Hypercholesterolaemia (yes/no)</td>
<td>1/9</td>
<td>8/3</td>
<td>–</td>
<td>0.1</td>
<td>(0.1–0.5)</td>
</tr>
<tr>
<td>Hypertriglyceridaemia (yes/no)</td>
<td>2/8</td>
<td>1/10</td>
<td>–</td>
<td>2.5</td>
<td>(0.2–32.8)</td>
</tr>
<tr>
<td>Heart disease (yes/no)</td>
<td>2/8</td>
<td>1/10</td>
<td>–</td>
<td>2.5</td>
<td>(0.2–32.8)</td>
</tr>
<tr>
<td>Smoking (yes/no)</td>
<td>4/6</td>
<td>7/4</td>
<td>–</td>
<td>0.4</td>
<td>(0.1–2.2)</td>
</tr>
</tbody>
</table>

AD, Alzheimer’s disease; aMCI, amnestic mild cognitive impairment; CI, confidence interval.
vascular risk factors presented: none or one vascular risk factor – two or more vascular risk factors; no difference was found in disease progression between the two groups (OR: 1.2; 95% CI: 0.2–6.8).

As regards the neuropsychological evaluation, subjects who converted to AD performed worse in the MMSE, Story Recall test, Attentional Matrices and Semantic Verbal Fluency Test than subjects in whom a diagnosis of aMCI was confirmed (P = 0.036, 0.002, 0.031 and 0.008 respectively; Mann–Whitney test) (Fig. 2). In addition, a further categorical analysis (< and >median) showed that a score beneath the median in Story Recall Test (P = 0.002; chi-squared test with Fisher’s correction), Token Test (OR: 8.2; 95% CI: 1–64.9), Copying Drawings (OR: 18.7; 95% CI: 1.6–222.9) and Semantic Verbal Fluency (OR: 32; 95% CI: 2.4–427.7) had a high predictive value in conversion to AD.

Discussion
We evaluated the clinical and socio-demographic characteristics, neuropsychological features, vascular risk factors and WMH in a group of subjects affected by aMCI. We carefully selected the group of aMCI subjects because our primary aim was to evaluate the eventual progression to AD and not to other kind of dementia. Several studies in the literature suggest that aMCI is more likely to progress to AD (3, 4). In our group, 47.6% of subjects converted to AD at the end of follow-up, while the remaining 52.4% remained stable. This result is in keeping with the progression rates reported from other studies, in which subjects were recruited from a clinical setting (24). None of the subjects in our study displayed an improvement in memory deficit, whereas population-based studies have reported reversible memory deficit over a 3-year period in 15–28% of cases. In this regard, discrepancies in conversion rates may be due to the manner in which subjects are recruited as well as to the use of different measures to operationalize the diagnostic criteria of aMCI.

Several studies have investigated the impact of various vascular risk factors on the incidence and prevalence of MCI (11, 25). By contrast, very few studies have analysed their contribution to the progression from MCI to dementia (26); moreover, the inclusion criteria may vary. In this regard, our perspective study may be considered to be one of the few that carefully selected its patients using the latest aMCI diagnostic criteria. In our population, subjects who converted to AD were more likely to be affected by hypertension, diabetes, hypertriglyceridaemia and heart diseases, though without reaching statistical significance. These results are in keeping with previous epidemiological studies, which have shown a relationship between vascular risk factors and AD (27–29), even though this relationship has yet to be fully understood (11, 26, 30). Moreover, in our study, aMCI subjects with hypercholesterolaemia were less likely to progress to AD. This result is in contrast to epidemiological studies which have highlighted the possible role of high blood cholesterol levels in the pathogenesis of both AD and MCI (9). Exactly how hypercholesterolaemia may increase the risk of AD is, however, still unknown. Several studies have shown that statins reduce the prevalence of AD (31, 32); in this regard, it is noteworthy that all the hypercholesterolaemic subjects included in our study were taking statins.

Several studies have found an association between arterial hypertension and WMH but we have not confirmed these data. This could be explained by the fact that the definition for arterial hypertension in our study included both high blood pressure measurements and antihypertensive medication intake. In this regard, it has been recently demonstrated (33, 34) that an active blood pressure-lowering regimen can stop or delay the progression of WMH.

We found no correlation between the WMH volume and conversion to AD. Data regarding this issue in the literature are discordant. Some authors have found that subjects affected by AD have a
higher incidence of WMH than controls (15, 28). By contrast, others have suggested that vascular pathology, as defined by WMH, and Alzheimer-type pathology, have specific, distinct cognitive correlates (35). Jicha et al. recently showed that the neuropathological outcome of aMCI following progression to dementia is heterogeneous and it includes AD at a high frequency; moreover, they suggested that vascular disease plays an important role in the progression from aMCI to dementia (36). We failed to confirm this last suggestion, probably due to the younger age of our population (89.5 years vs 72.6 years) and to the fact that we excluded both large vessel infarcts and lacunar infarcts larger than 5 mm. Therefore, we hypothesize that the progression from aMCI to AD in our population is merely the expression of the underlying neurodegenerative Alzheimer-type pathology. This is in agreement with recent data which suggest that the neuropathological features of aMCI match the clinical features and seem to be intermediate between the neurofibrillary changes of ageing and the pathological features of very early AD (37). Hence, this suggests that vascular risk factors and WMH do not, particularly in the early phases of cognitive impairment, influence the course of disease. From this point of view, WMH may be considered as a superimposed factor resulting from ageing (38).

One limitation of our study is the lack of other MRI measures such as hippocampal volume and diffusibility, entorhinal cortex or global brain atrophy that are currently considered as possible markers of progression from MCI to dementia. Some authors showed that smaller hippocampi (39) or a higher hippocampal mean diffusivity (40) are associated with an increased risk for conversion, and that different patterns of grey matter density distribution may be associated with different rates of conversion to AD (41).

Our results show that the only real predictors of conversion from aMCI to AD are the subjects’ performance in neuropsychological assessment. Our data are in agreement with those of other authors who have shown that the severity of a memory deficit, particularly if associated with a low performance in another cognitive domain, may predict progression to dementia (1, 4, 42). We show that low scores, although within the normality, obtained at Semantic Verbal Fluency Test and at Attentional Matrices may predict the conversion to AD. Thus, in an overall assessment of the risk of conversion from aMCI to AD, doctors should estimate not only the severity of the memory deficit but also any borderline cognitive performances.

In conclusion, although the low numerosness of the sample, our results show that aMCI criteria, if strictly applied, identify a category of subjects who are likely to develop AD. Although WMH does not appear to play a role in progression from aMCI to AD, some vascular risk factors do seem to promote it. Lastly, our work further confirms the need for an accurate neuropsychological assessment not only to correctly classify MCI clinical subtypes but also to predict the eventual progression to AD more accurately.

References


