Does vascular burden contribute to the progression of MCI to dementia?

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Supplementary Files

Supplemental methods

Study Population

Out of 1,931 eligible subjects, 257 fulfilled the inclusion and exclusion criteria for a clinical diagnosis of MCI and were included in the study. In the remaining cases the following diagnosis were made: 927 patients with Alzheimer's disease (including 327 cases with associated cerebrovascular disease), 195 patients with vascular dementia, 75 patients with Lewy body dementia, 39 patients with fronto-temporal dementia, 8 subjects with primary progressive aphasia, 12 patients with cortico-basal degeneration, 77 patients with severe dementia of unspecified origin, 5 patients with AIDS dementia complex, 4 patients with Huntington's Corea, 1 Creutzfeldt-Jakob disease patient, 46 subjects with psychiatric disorders, 153 subjects with subjective cognitive complaints. Finally, the diagnosis was not made in 132 subjects, who did not perform the required exams.

Follow-up procedure

Patients who, at any time during follow-up, did not present themselves for the scheduled examination were contacted by phone and proposed a new appointment date. If a subject refused or was unable to undergo the follow-up visit, information on clinical status was collected by phone from an informant and the dementia screening was performed using the Clinical Dementia Rating (CDR)[1], as previously described[2]. The phone call was performed by the same neurologist (FC) who assigned the CDR score.

Data collection

Global cognitive function was assessed using the Mini Mental State Examination (MMSE)[3] and the Clinical Dementia Rating (CDR)[1] scores. Neurofunctional status was assessed with Basic[4] and Instrumental[5] Activities of Daily Living (BADL, IADL). Somatic diseases were ascertained

by self-report and medications use, and were coded according to International Classification Disorder tenth-edition (ICD-10). Multimorbidity was assessed using the Cumulative Illness Rating Scale[6]. The presence of depression was assessed using the 30-item version of the Geriatric Depression Scale **(GDS)** [7].

Neuropsychological assessment

In order to define the pattern and degree of cognitive impairment, all subjects underwent a standard neuropsychological battery [8] with the following tests: MMSE , Raven progressive matrices colored 47, digit span, Corsi Block Tapping Test, Rey complex figure copy and recall, story recall, Weigl's test, frontal assessment battery, number cancellation test, word fluencies (phonemic fluency and category fluency), clock drawing test. The tests were administered in a standard sequence, alternating verbal and non-verbal tests. The test sequence was also decided according to the memory tests risk contamination, so that no test with content that could affect performance on a memory test was administered between immediate and delayed recall. All test scores were adjusted for each subject age and educational level.

Exclusion criteria

Exclusion criteria for MCI were: a) dementia, defined according to the Diagnostic and Statistical Manual of Mental Disorders DSM-IV [9]; b) other psychiatric disorders [9]; c) organic brain pathology or organic illness affecting the brain according to the ICD-10; d) significant history of head injury; e) major systemic illnesses or medical complications, including vitamin deficiency states, thyroid disorders, and sensory disorders (i.e., blindness or deafness); f) history of drug or alcohol dependence; g) structural brain alterations that included mass lesions and hydrocephalus.

Baseline assessment of vascular burden

The assessment of vascular burden was performed with the following standardised protocol.

Vascular risk factors

Smoking habits were ascertained through self-reports. Body mass index was calculated as weight in kilograms divided by the square of the height in meters. Sitting blood pressure (BP) measurement was recorded with the participant at rest. Systolic and diastolic BP was measured in the right arm, using a standard sphygmomanometer and stethoscope, after five-minutes of rest. Fasting venous plasma glucose and total cholesterol levels were determined using standard enzymatic techniques.

ApoE genotype was determined at the IRCCS Fondazione Ospedale Maggiore Policlinico University of Milan (DG and ES) by polymerase chain reaction-restriction fragment length polymorphism technique.[10]

Vascular diseases

The diagnosis of cerebrovascular and cardiovascular diseases was based on participants or relatives interviews, supplemented by a neurological examination or review of medical records. Both colour Doppler ultrasound and electrocardiogram were performed.

Vascular Summary Scores

The Framingham Stroke Risk Profile (FSRP)[11,12] is a clinical estimate of the cumulative burden of risk factors for cerebrovascular disease. The components of the FSRP are: sex, age, systolic BP, the use of antihypertensive therapy, diabetes mellitus, cigarette smoking, prior cardiovascular disease (coronary heart disease, cardiac failure, or intermittent claudicatio), atrial fibrillation, and left ventricular hypertrophy (as assessed by electrocardiogram). The total points allotted can range from 1 to 30.

The Hachinski Ischemic Score (HIS) [13] is a clinical index estimator of cerebrovascular disease burden, used in the specific context of estimating the vascular contribution to the clinical picture in a person with dementia. The items include: abrupt onset, stepwise deterioration, fluctuating course, nocturnal confusion, depression, emotional incontinence, history of hypertension, evidence of atherosclerosis, history of stroke, neurological symptoms and signs, preservation of personality and somatic complaints. The total score can range from 0 to 18. A score < 4 is considered indicative of the absence of significant cerebrovascular disease burden while a score ≥ 7 suggests a significant vascular burden[14].

White Matter Lesions

Brain computed tomography and magnetic resonance were analysed by a neurologist (LM) specifically trained for the study and blinded to clinical diagnosis. The Age-Related White Matter Changes[15] scale was used to rate subcortical cerebrovascular disease. This is a four-point scale that rates white matter changes separately in five areas: frontal, parieto-occipital, temporal, infratentorial/cerebellum and basal ganglia (striatum, globus pallidus, thalamus, internal/external capsule and insula). The first three areas are scored as 0= no lesions, 1=focal lesions, 2=beginning confluence of lesions, 3=diffuse involvement of the entire region, with or without involvement of U fibers. The infratentorial/cerebellum and basal ganglia are scored as 0=no lesions, 1=only one focal lesion (>5mm), 2=more than one focal lesion, 3=confluent lesions. The final result of the rating is 10 separate scores (five for the right and five for the left hemisphere) ranging between 0 and 3, rating the different brain regions.

Data Analysis

Missing information on APOE genotype was estimated using multiple imputation [16], **which assigned 0 (carrying no ε4 allele) or 1 (being a carrier of at least one ε4 alleles). The procedure consisted of three steps: first, gender, age and available APOE data were used as predictors to**

generate five plausible estimates of the missing values, which were stored in five different datasets; second, independent data analysis was carried out on each complete dataset to calculate incidence rates; finally, the different incidence estimates were pooled together according to Rubin's formula.

Supplementary Analyses

GDS. **In a subgroup of 189 subjects who underwent the GDS [7], we found no statistically significant difference in the GDS mean score between the subjects who were still in the MCI category at the end of the surveillance and those who have progressed to dementia (10.3 ± 6.1 vs. 10.0 ± 7.0; p=0.8).**

Brain Imaging. **All MCI subjects underwent either brain computer tomography (CT) (125 subjects; 51%) or magnetic resonance (MR) (121 subjects; 49%). MR was superior to CT in identifying cortical lesions, which were detected in 66 out of 125 (53%) subjects evaluated with CT vs. 96 out of 121 (79%) subjects evaluated with MR (p=0.001). In accordance with the literature [15] this difference was mainly attributable to the higher sensitivity of MR to parieto-occipital lesions (CT 38% vs. MR 60%; p=0.003). On the other hand, the sensitivity of the two methods to subcortical lesions did not differ: they were detected in 37 (30%) subjects evaluated with CT and in 45 (37%) subjects evaluated with MR. Analogously, the sensitivity of the two methods to infratentorial lesions did not differ: they were detected in 5 (4%) subjects evaluated with CT and in 11 (9%) subjects evaluated with MR.**

CDR. **Out of 257 MCI subjects included in the study, 12 (4.7%) neither performed the follow-up visit nor answered to the telephone call (and they were excluded from the analyses) and 31 (12.6%) had an informant who answered to the telephone interview, even if they refused the follow-up evaluation (and they were included in the analyses). They were diagnosed as having dementia if their CDR [1] score changed from 0.5 to greater than or equal to 1 (14 cases), and they were classified as stable MCI if the CDR was still equal to 0.5 at the end of dementia**

surveillance (17 cases). Out of the 14 stable MCI subjects, 13 have died (one for a hemorrhagic stroke) during dementia surveillance.

Sensitivity analysis. The main data analyses were repeated after excluding the 31 subjects with dementia diagnosis based on informant interview, with the following results: subjects with deep WMLs and high (≥4) HIS scores had a 3.3-fold (95% IC: 1.5-7.5) increased risk of progressing to dementia, and subjects with deep WMLs and high (≥14) FSRP scores had a 2.1-fold (95% IC: 1.2-3.7) increased risk of progressing to dementia.

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