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The metabolic syndrome in a memory clinic population: Relation with clinical profile and prognosis

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ABSTRACT

Background: The metabolic syndrome (MetS) refers to a cluster of cardiovascular risk factors that is associated with an increased risk of cognitive impairment and dementia. It is unclear however, if the presence of the MetS is associated with a particular clinical profile or a different prognosis in patients with cognitive complaints or early dementia.
Objectives: To compare 1) the clinical profile and 2) the prognosis of patients attending a memory clinic according to the presence or absence of MetS.
Design: Longitudinal cohort.
Setting: Memory clinic.
Participants: We included and followed 86 consecutive patients (average age of 66.7 (SD 9.7)) from the Amsterdam Dementia Cohort with an MMSE > 22.
Measurements: Clinical profile (neuropsychological examination, brain MRI, cerebrospinal fluid (CSF) biomarkers, clinical diagnosis) on an initial standardized diagnostic assessment was compared according to MetS status. Progression to dementia was assessed in initially nondemented patients (subjective complaints n = 40, mild cognitive impairment n = 24, follow-up available in 59).
Results: 35 (41%) patients met the MetS criteria. Demographics were similar between patients with or without the MetS. At baseline, diagnosis, cognitive performance, severity of degenerative or vascular abnormalities on MRI, and CSF amyloid and tau levels did not differ between the groups (all $p > 0.05$). Among nondemented patients, however, MetS was associated with worse performance on executive function, attention & speed and visuoconstructive ability (z-scores, $p < 0.05$). During a mean follow-up of 3.4 years a similar proportion of patients with (4; 17%) and without (6; 17%) the MetS progressed to dementia ($p = 0.45$).
Conclusion: Among nondemented patients presenting at a memory clinic MetS was associated with slightly worse cognitive performance (worse on tasks assessing executive functions, visuo-constructive ability, attention & speed), but conversion rate to dementia was not increased.

1. Introduction

Cardiovascular risk factors are associated with an increased risk of dementia, which accounts for both Alzheimer's disease and vascular dementia (review: [1]). Cardiovascular risk factors frequently co-occur. This clustering of risk factors has been captured by the concept of metabolic syndrome (MetS), which is defined as the presence of three or more of the following components: impaired glucose tolerance, obesity, hypertension, hypertriglyceridemia, and reduced high-density lipoprotein cholesterol [2]. The MetS and each of its components are associated with impaired cognitive performance and an increased risk of dementia (reviews: [3,1]).

The strength of the association between MetS and dementia is dependent on the number of MetS components that is present in an

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individual [4], where the cumulative influence of multiple components is greater than the sum of its individual components [5]. The underlying mechanism of the association between MetS and dementia is, however, still uncertain. Epidemiological studies consistently link MetS with vascular dementia, while contrasting findings exist on the presence of an association between MetS and Alzheimer's disease (review: [6]). Hence, the association between MetS and dementia might be due to an acceleration of neurodegenerative changes, vascular lesions, or both. Furthermore, it is uncertain if the presence of MetS is associated with a faster progression of cognitive impairment [7,8].

Unravelling the nature of the relation between MetS and cognitive dysfunction will help in the development of potential prevention or treatment strategies. The first objective of this study was to determine whether patients with or without the MetS differ in their clinical profile (i.e. clinical diagnosis, cognitive performance, brain MRI abnormalities and cerebrospinal fluid (CSF) biomarkers) at first presentation at a memory clinic. The second aim was to evaluate whether the MetS is associated with the prognosis of these patients.

2. Patients and methods

2.1. Study population

Patients were included from the memory clinic based Amsterdam Dementia Cohort of the VU University Medical Centre (VUmc). Patients received a standardized one day diagnostic assessment including an interview on medical history, medication use and education level, a physical examination, neurological examination, extensive neuropsychological testing, an MRI-scan of the brain and blood tests. Clinical diagnoses were made at a multidisciplinary consensus meeting based on internationally established diagnostic criteria, without knowledge of the CSF biomarker results.

The medical records of all patients who were evaluated at the memory clinic for the first time between 01/08/2004 and 30/06/2006 were examined and followed until 01/01/2012. Patients from the following four diagnostic categories were eligible for this study: 1) possible or probable Alzheimer's disease [9], 2) vascular dementia [10], 3) mild cognitive impairment [11], and 4) subjective complaints without cognitive impairment on neuropsychological assessment (subjective cognitive complaints, i.e. criteria for mild cognitive impairment not fulfilled and no psychiatric diagnosis). We selected all patients who were at least 45 years of age, had a Mini Mental State Examination (MMSE) score above 22 (n = 108), and from whom sufficient data was available to establish the presence or absence of MetS (i.e. either the presence or absence of at least three out of the five risk factors). This resulted in a study population consisting of 86 patients.

2.2. Biologic samples

Plasma fasting glucose, high-density lipoprotein cholesterol and triglyceride levels were determined at the Department of Clinical Chemistry of the VUmc. For Apolipoprotein E (ApoE) genotyping, DNA was isolated from 10 ml EDTA blood by the QIAamp DNA blood isolation kit from Qiagen. ApoE genotype was determined with the light cycler ApoE mutation detection method (Roche Diagnostics GmbH, Mannheim, Germany). Subjects were classified as ApoE ε4 carriers if they had one or two ε4 alleles, and as non-carriers if they had no ε4 alleles.

All patients who are eligible for a lumbar puncture were offered CSF analyses as part of their evaluation. CSF was obtained by lumbar puncture between the L3/L4 or L4/L5 vertebra, using a 25-gauge needle, and collected in 10 ml polypropylene tubes. CSF levels of amyloid β 1–42 (Aβ42), tau and tau phosphorylated at threonine 181 (p-tau) were measured by commercially available sandwich ELISA (Innotest β-amyloid, Innotest hTAU-Ag, and Innotest Phosphotau; Innogenetics, Ghent, Belgium), as described previously [12]. The team involved in the CSF analysis was not aware of the clinical diagnoses. CSF was available for n = 45. Patients who did not undergo a lumbar puncture did not differ in sociodemographic characteristics, MMSE score and clinical diagnosis from those who did.

2.3. Definition of the metabolic syndrome

MetS was defined according to the National Cholesterol Education Program/Adult Treatment Panel III (NCEP/ATPIII) criteria revised AHA/NHLBI [2]. Patients were considered to have MetS if they met three or more of the following five criteria: 1) plasma glucose ≥ 6.1 mmol/l or antidiabetic drug use, 2) triglyceride concentration ≥ 1.69 mmol/l or antihypertriglyceridemia drug use; 3) high-density lipoprotein cholesterol < 1.29 mmol/l in women and <1.03 mmol/l in men; 4) blood pressure ≥ 130/85 mm Hg or antihypertensive drug use; and 5) obesity, because waist circumference was not measured at the time of data acquisition, it was substituted by BMI > 27 in women and BMI > 29 in men [13]. Even with missing data on one or two MetS components, the presence or absence of MetS could be established for patients in whom at least three risk factors from the metabolic syndrome could be classified as absent (without MetS) or three as present (MetS).

2.4. Neuropsychological examination

MMSE was used as measure of global cognitive function. Memory was assessed with the Rey Auditory 15-word Verbal Learning Test and the Visual Association Test [14,15]. Language was assessed using animal fluency (60 s) and Visual Association Test object naming [14]. Furthermore, speed & attention was assessed with the Trail Making Test A, the forward condition of Digit Span and Stroop cards I and II [16–18]. Executive functioning was tested by the third card of the Stroop test, the Trail Making Test B and the backwards condition of Digit Span [16–18]. Visuoconstructive abilities were tested by the Rey–Osterrieth Complex Figure Test [19]. All neuropsychological data were standardized into z-scores. The scores on the Trail Making Test and Stroop were inverted by computing −1 * z-score, because higher scores imply a worse performance. In order to create the five cognitive domains, the mean z-scores of the available tests in every domain were calculated.

Depressive symptoms were assessed by the Geriatric Depression Scale, a questionnaire specifically developed as a screening instrument for the presence of depressive symptoms in older populations [20].

2.5. Brain imaging

MR imaging was performed on a 1.0-T Siemens Magnetom Impact Expert scanner (Siemens AG, Erlangen, Germany) and included coronal T1 and T2-weighted 3D MPRAGE volumes (magnetization prepared rapid acquisition gradient echo; single slab 168 slices; matrix 256 × 256; FOV 250 mm; voxel size 1 mm × 1 mm × 1.5 mm; repetition time = 15 ms; echo time = 7 ms; inversion time = 300 ms; and flip angle 15) and a fast fluid attenuated inversion recovery sequence (axial, 5-mm contiguous slice, and 1-mm in-plane resolution). Three patients did not undergo an MRI.

2.5.1. Visual rating

Medial temporal lobe atrophy (MTA) was evaluated by using a visual rating scale [21] on coronal T1-weighted images based on the choroid fissure width, the temporal horn width, and the hippocampal height (possible range of scores for each side, 0 to 4). Scores of the right and left sites were averaged. Lacunes were defined as T1-hypointense and T2-hyperintense CSF-like lesions that were surrounded by white matter or subcortical gray matter and not located in areas with a high prevalence of widened perivascular spaces (e.g., anterior commissure region) [22]. White matter lesions (WML) were rated according to a slight modification of the Scheltens rating scale [23] and divided in periventricular