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Cognitive functioning among patients with diabetic foot

Anna Marseglia [a,b,*], Weili Xu [a,*], Debora Rizzuto [a], Camilla Ferrari [a,c], Christine Whisstock [d], Enrico Brocco [d], Laura Fratiglioni [a,e], Gaetano Crepaldi [b,d], Stefania Maggi [b,d]

[a] Aging Research Center, Karolinska Institutet and Stockholm University, Stockholm, Sweden
[b] Institute of Neuroscience – Aging section, Italian National Council Research (CNR), Padua, Italy
[c] Department of Neuroscience, Psychology, Drug Research and Child Health (NEUROFARBA), University of Florence, Florence, Italy
[d] Leonardo Foundation and Diabetic Foot Unit, Policlinico Abano Terme, Abano Terme, Italy
[e] Stockholm Gerontology Research Center, Stockholm, Sweden

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ABSTRACT

Aims: Using diabetic foot (DF) as an indicator of severe diabetes, we aimed to investigate the cognitive profile of DF patients and the relations between cognitive functioning and both diabetes complications and comorbidities.
Methods: Dementia-free patients with DF aged 30–90 (n = 153) were assessed through medical records and a cognitive battery. Information on diabetes complications and comorbidities was collected via interview; glycated hemoglobin (HbA1c) was tested. Data were analyzed using robust logistic or quantile regression adjusted for potential confounders.
Results: The mean Mini-Mental Examination (MMSE) score of patients was 24.6 (SD = 3.6), and 40% had global cognitive dysfunction (MMSE ≤24). Among elderly patients (aged ≥65), MMSE impairment was related to amputation (OR 3.59, 95% CI 1.07–12.11). Episodic memory impairment was associated with foot amputation (OR 4.13, 95% CI 1.11–15.28) and microvascular complications (OR 9.68, 95% CI 1.67–56.06). Further, elderly patients with HbA1c <7% had increased odds of psychomotor slowness (OR 7.75, 95% CI 1.55–38.73) and abstract reasoning impairment (OR 4.49, 95% CI: 1.15–17.46). However, such significant associations were not shown in adult patients aged <65.
Conclusion: Amputation, microvascular diseases and glycemic control were associated with impaired global cognitive function and its domains among patients aged ≥65.

1. Introduction

Type 2 diabetes mellitus (T2DM) is the most common form of diabetes and affects about 285 million people worldwide (Chen, Magliano, & Zimmet, 2012). Chronic high glucose levels may cause damage to nerves and blood vessels that can result in diabetic retinopathy, nephropathy, peripheral neuropathy, and vascular diseases (Brown, Reynolds, & Bruemmer, 2010).

An increasing number of studies show that diabetes is a risk factor for both vascular dementia and Alzheimer's disease (Biessels, Staekenborg, Brunner, Brayne, & Scheltens, 2006) and that diabetes may accelerate progression from mild cognitive impairment to dementia (Xu et al., 2010). T2DM is also associated with poor performance in cognitive tasks involving attention, executive functions, episodic memory, psychomotor speed, and visual-constructive skills in people without dementia (Kohler et al., 2012; van den Berg et al., 2010). However, findings are inconsistent, and the specific cognitive domains affected by T2DM remain unclear (Arvanitakis, Wilson, Li, Aggarwal, & Bennett, 2006; Yeung, Fischer, & Dixon, 2009). Although several studies have investigated the possible influence of diabetes complications on cognition, the cognitive characteristics of patients with longstanding diabetes are not well known (Kloos et al., 2009).

Diabetic foot (DF) is one of the most common T2DM complications; it derives from the combination of neuropathy and vascular disease. Diabetic foot includes skin infection, ulceration, and even destruction of deep tissues that may lead to foot amputation. In recent years, it has become clearer that a foot ulcer is indicative of severe diabetes. Studies in both hospital settings and primary care indicate that individuals with diabetic foot ulcers have much more severe diabetic complications than those without foot ulcers (Iversen et al., 2009). DF is the leading cause of non-traumatic amputation throughout the world (Frykberg et al., 2006). Some reports described high prevalence of cognitive impairment among individuals with lower limb amputation, which suggests that amputees may be particularly susceptible to cognitive decline (Coffey, O'Keeffe, Gallagher, Desmond, & Lombard-Vance, 2012; Phillips, Mate-Kole, & Kirby, 1993).

Abbreviations: CI, Confidence interval; DF, Diabetic foot; DFP-CoDe, Diabetic Foot Patients—Cognition and Depression; IWGDF, International Working Group on Diabetic Foot; MMSE, Mini-Mental State Examination; TMT–A, Trial Making Test part A; TMT–B, Trial Making Test part B; TMT B-A, Trial Making Test part B minus A; RAVLT, Rey Auditory Verbal Learning Test; OR, Odd ratio; SD, Standard deviation; T2DM, Type 2 diabetes mellitus.

Conflict of interest: The authors declare that there is no conflict of interest.

* Corresponding authors at: Aging Research Center, Karolinska Institutet, Gävlegatan 16, SE 113 30 Stockholm, Sweden. Tel.: +46 8 690 5848; fax: +46 8 690 6889.
E-mail addresses: Anna.Marseglia@ki.se (A. Marseglia), Weili.Xu@ki.se (W. Xu).

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The present study used data from the Diabetic Foot Patients—Cognition and Depression (DFP-CoDe) project to achieve two aims; throughout the study, diabetic foot was used as an indicator of severe diabetes. First, we aimed to assess the cognitive profile of people with DF. Second, we sought to examine the relationship between cognitive functioning and diabetic complications and comorbidities taking glycemic control into account.

2. Subjects

DFP-CoDe is a cross-sectional study on cognitive functioning and psychological disease in dementia-free patients with diabetic foot. From April 2009 to July 2011, a total of 169 cognitively healthy inpatients and outpatients undergoing treatment for DF at the Diabetic Foot Operative Unit of a hospital in the Veneto region of Italy were consecutively enrolled in this study. Inclusion criteria included presence of T2DM, history of diabetic foot ulcers or amputation, age >18, and no history of disabling stroke or dementia. History of stroke and dementia was ascertained from medical records, self-report, and proxy-reports. Of the 169 patients, 16 declined to participate; this left 153 participants in the current study. Written informed consent was obtained from all participants. This study was approved by the Regional Ethical Committee of Padua, Italy.

3. Materials and methods

3.1. Data collection

Data on age, sex, education, occupation, lifestyle (alcohol use and smoking), and drug use were collected through an interview that followed a structured questionnaire. Education was defined as the maximum years of formal schooling and dichotomized as "low education" (≤8 years) and "high education" (>8 years) in accordance with previous studies and the Italian educational system (Qiu, Backman, Winblad, Aguero-Torres, & Fratiglioni, 2001). Occupation was dichotomized into manual jobs vs. intellectual jobs. Alcohol was categorized into "no," "current," and "former" consumption of wine, beer or spirits. Cigarette smoking was grouped as "current smoking," "quit smoking," and "never smoked." Information on medical history and medication use was ascertained on the basis of combined information from medical records, self-report, and the reports of proxies such as partners and relatives. For outpatients, information on medical history and treatments was collected during a personal interview. Information on type of diabetes, age at onset, family history of diabetes, treatment, and diabetes-related complications and comorbidities was derived from medical records. Diabetic complications included microvascular complications, neuropathy and amputation. Microvascular complication included a history of diabetic retinopathy or kidney disease; the variable was dichotomized (absence vs. presence). Amputation and neuropathy were dichotomized as well (absence vs. presence). Comorbidities were defined as a history of hypertension, heart disease, or non-disabling stroke/transient ischemic attack (TIA). The variable was dichotomized (absence vs. presence). Mood was assessed in all participants using the Italian version of the Beck Depression Inventory-2nd Edition (BDI-II) (Beck, Steer, & Brown, 2007), and the variable was dichotomized into absence (BDI-II <13) vs. presence (BDI-II ≥13) of depressive symptoms (Beck et al., 2007).

3.2. Assessment of DF and glycemic control

T2DM was ascertained on the basis of information from medical records, use of oral hypoglycemic agents and/or insulin, or medical examination in accordance with standard diagnostic procedure (American Diabetes Association, 2010).

Diabetic foot is a condition that frequently leads to pathologic consequences such as infection, ulceration, or destruction of deep tissues. It is associated with neurologic abnormalities, various degrees of peripheral vascular disease, and/or metabolic complications of diabetes in the lower limbs (Frykberg et al., 2000). The diagnosis was based on clinical examination and medical records in accordance with standard guidelines (IWGDF 2007) (Apelqvist, Bakker, van Houtum, Nabuurs-Franssen, & Schaper, 2000; Apelqvist, Bakker, van Houtum, & Schaper, 2008).

Blood samples were taken from all the participants. Glycosylated hemoglobin (HbA1c) was measured using Tina-quant Hemoglobin A1c Gen. 2 method. HbA1c level (%) was used as a marker of glycemic control and classified into three groups on the basis of recent data from a randomized clinical trial (Gerstein et al., 2008): controlled, HbA1c <7% (<53 mmol/mol); borderline controlled, HbA1c 7–8% (53–64 mmol/mol); and, uncontrolled HbA1c >8% (>64 mmol/mol), T2DM.

3.3. Cognitive assessment

All participants underwent a neuropsychological evaluation with tests that were administered in a fixed order by a trained neuropsychologist. The tests took approximately 30 minutes. Global cognitive function was assessed using the Mini-Mental State Examination (MMSE) (Folstein, Folstein, & McHugh, 1975); MMSE score ≤24 was defined as general cognitive function impairment (Kivipelto et al., 2001). Four specific cognitive domains, including processing speed, executive function, episodic memory, and abstract reasoning, were evaluated through the following neuropsychological tests: the Trail Making Test—part A and part B (TMT-A and B) (Mondini, Mapelli, Vestri, & Bisiacchi, 2003); the Rey Auditory Verbal Learning Test (RAVLT), immediate and delayed recall (Carlesimo, Caltagirone, & Gainotti, 1996); and the Raven Colored Progressive Matrices (Splinner & Tognoni, 1987). Impairment in cognitive domains was defined in accordance with established cut-offs in each specific test for an Italian population (Ashendorf et al., 2008; Carlesimo et al., 1996; Liepelt-Scarfone et al., 2011; Mondini et al., 2003; Splinner & Tognoni, 1987).

TMT-A was used to assess processing speed. A z-score was calculated using mean and standard deviation from the normative sample, and a z-score >1.50 indicates processing speed impairment (Ashendorf et al., 2008; Liepelt-Scarfone et al., 2011). The executive function domain included divided attention, measured using TMT-B, and mental flexibility, calculated as TMT-B time minus TMT-A time (TMT B-A). Executive function impairment was defined as impairment in one or both components (divided attention and mental flexibility). Immediate and delayed recall tasks from RAVLT were used for the episodic memory domain. The immediate recall task tested verbal short-term memory, and the delayed recall task tested learning rates. Memory impairment was defined as immediate recall of <28.53 and/or delayed recall of <4.69. Abstract reasoning impairment was defined as a Raven score of <21.

3.4. Statistical analyses

The characteristics of adult (aged <65) and elderly (aged ≥65) participants were compared using independent t-tests for continuous variables and chi-square tests for categorical variables. Fisher's exact test was used when sample sizes were small (<20). Before each t-test, Shapiro–Wilk's test was used to verify the normality assumption, and Levene's test was used to verify the variance homogeneity assumption. Welch's t-test was used for normally distributed variables that had unequal variance. Non-parametric quantile regression with interquantile range (IQR) was applied when the two populations were not normally distributed (Buchinsky et al., 1995).

Logistic regression analyses were used to estimate the odds ratios (ORs) with 95% confidence intervals (95% CIs) of impairment in general cognitive function and in the cognitive domains of executive