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Cognitive function may be a predictor of retinopathy progression in patients with type 2 diabetes.

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Abstract

Background and aims.

Micro-and macrovascular complications of diabetes, such as retinopathy and nephropathy progress over time and may be associated with cognitive decline. In this paper we aimed at gaining further insight into the association between cognitive function and retinopathy in type 2 diabetes.

Methods and results.

Observational 8-year prospective study of 498 outpatients. Demographic and clinical variables were monitored, along with retinopathy, depression, anxiety and cognitive function. Baseline fundus photographs were available in 477 patients, 240 with no retinopathy, 110 with mild, and 127 with moderate/more severe retinopathy. Of the first two groups, 279 patients were re-evaluated after 8 years, of whom 181 still had no/mild retinopathy and 98 had progressed to more severe stages. On multivariate analysis, retinopathy progression was associated with being insulin treated (p=0.036), and worse cognitive function (p=0.025) at baseline.

Conclusions.

Cognitive function may be an independent predictor of retinopathy progression.

Introduction.

Most clinical studies showed a direct correlation between glycemic control over time and incidence and progression of Diabetic Retinopathy (DR) in type 2 diabetes (1). Type 2 Diabetes Mellitus (T2DM) is predominantly managed during daily life by the persons with the disease and/or their care providers. Since adequate treatment of diabetes depends on patients' adherence to demanding lifestyle and medication regimens, cognitive factors may play a critical role in its management.

We reported previously on prevalence and progression over 8 years (2) of depression, anxiety and cognitive function in a cohort of patients with T2DM. In this subanalysis, we investigated the possible clinical and psycho-cognitive predictors of DR progression in the same cohort.

Materials and Methods.

Design

Four-hundred and ninety-eight outpatients with type 2 diabetes, 249 on insulin treatment (IT) and 249 on other agents (NIT) were enrolled in an observational prospective study. Their detailed baseline clinical and psycho-cognitive data were reported previously (2). Patients were mostly Caucasian aged 40-80, routinely followed in urban diabetes clinics. Exclusion criteria were history of psychiatric illnesses in the patients or their families, presence of cancer, renal replacement therapy or other life-limiting chronic conditions.

Eight years later, the patients were invited to a follow-up visit, to which they gave their informed consent in accordance with the Declaration of Helsinki principles. Details of those lost to follow-up or dead were reported in detail elsewhere (2). Data on age, gender, schooling, occupation, family status, smoking status, self monitoring of blood glucose, family history and duration of diabetes, body weight, HbA1c (HPLC, according to IFCC), fasting blood glucose (glucose-oxidase), blood pressure, serum creatinine, total and HDL cholesterol, triglyceride were collected.

Fundus examination was by 2-field, 45° digital colour photography, using a Canon CR6-45NM fundus camera (Canon Inc, Ochigiken, Japan). Retinopathy was classified as absent if corresponding to ETDRS standard 10, mild if doubtful or ETDRS =20, and moderate or more severe if ETDRS ≥35 (3). Grading of the worse eye was considered to assign severity.

Cognitive Assessment

Cognitive performance was evaluated by Mini Mental State Examination, (MMSE) (4), administered as a semi-structured interview. Median reference scores change with age, ranging from 29, for individuals 18 to 24 years of age, to 25 for those aged 80 years and older, and years spent in formal education, ranging from 29 for individuals with ≥9 years of schooling, 26 for those with 5-8 years, to 22 for those with 0-4 years of schooling. Depression and anxiety were assessed

by the Zung Self-rating scales (5). All tools had been translated into Italian and revalidated. If the patients had literacy problems, the questionnaires were completed with the help of a health operator.

Statistical Analysis.

Descriptive data are shown as absolute frequencies of the different modalities for categorical data and as mean ± standard deviation for continuous variables. T-test for continuous variables and chi-square or Fisher exact test for qualitative variables were carried out to compare data at baseline of possible predictors of DR after 8 years for patients with no or mild retinopathy at 8 years and patients who developed moderate-severe retinopathy. In order to adjust for the relative effect of each predictor of the development of severe DR, retinopathy after 8 years (moderate-severe vs no-mild) was inserted as the dependent variable in a logistic regression model, where clinical and psycho-cognitive data at baseline, i.e. age, gender, glucose lowering treatment (IT vs NIT), HbA1c, retinopathy (mild vs none), depression, anxiety and MMSE scores, were originally inserted as independent variables. After testing for interaction between HbA1c and retinopathy we decided to insert in the model the two composite variables representing HbA1c with no retinopathy and the other with HbA1c and mild retinopathy. Depression and anxiety were intercorrelated with MMSE but didn't show any significant relation with retinopathy after 8 years follow up, therefore were dropped out of the model. The final model is shown in Table 1.

Significance level was set at $\alpha=0.05$. All analyses were performed with Stata 13.

Results

Out of 477 patients for whom fundus evaluation was available at baseline, 240 (160 IT and 80 NIT) had no DR and 110 (48 NIT and 62 IT) had mild non proliferative DR. Another 127 (24 NIT and 103 IT) already had moderate or more severe DR at baseline and therefore were not considered in this analysis. Of the first two groups, 279 (80%) patients could be re-evaluated at 8 years, of whom 181 had no or mild DR and 98 had progressed to moderate/more severe DR.

The 98 patients who progressed to moderate/more severe DR were older (66.4 ± 6.9 vs 66.3 ± 8.2; p=0.032), more likely to be on insulin treatment (46 NIT/52 IT vs 119 NIT/62 IT; p=0.003), practised more frequent self-monitoring of blood glucose (p=0.024), had higher HbA1c (8.30% ± 1.2 vs 7.87% ± 1.03 or 67.19 ± 13.16 vs 62.60 ± 14.26 mmol/mol; p=0.009) and lower MMSE scores (24.24 ± 3.47 vs 25.37 ± 3.76; p=0.017) at baseline. On multivariate analysis (Table 1), being on insulin treatment (OR 1.91, 95%CI 1.04;3.50, p=0.036) and having higher HbA1c in patients with mild DR at baseline (OR 1.45, 1.13;1.85, p=0.003) were associated with progression to moderate or more severe DR, whereas male gender (OR 0.49, 0.27;0.90, p=0.021) and a higher MMSE score (indicative of better cognitive ability) (OR 0.90 per score point; 0.83;0.99, p=0.025) were protective.

Discussion.

In this longitudinal observation, DR progression over 8 years was more likely to occur in older insulin treated individuals with worse metabolic control and lower cognitive performance at baseline, suggesting that, in patients with long-lasting diabetes, microvascular damage may simultaneously affect the retina and the brain, both parts of the central nervous system with common anatomical origins and structure.

Previous research on the links between retinopathy and cognitive impairment is mostly in the direction of the former preceding or predicting the latter (6), whereas our results suggest that the relationship may be bi-directional. An association between advanced diabetic retinopathy and risk of cognitive decline or overt dementia was reported (7,8), and cerebral microbleeds and retinal microvascular signs were related to evidence of vascular cognitive impairment (9). Others found that the risk of mild cognitive impairment may be more than doubled if diabetic retinopathy is present (10). A recent systematic review reported an association between cognitive impairment and diabetic retinopathy, although only in older males or patients with established macrovascular disease (11). Indeed, both retinopathy and cognitive impairment share a number of risk factors with large vessel disease, such as hypertension and dyslipidemia (12) and, although in this paper MMSE scores predicted later progression of diabetic retinopathy independently of hypertension and serum cholesterol or triglyceride, a contribution of these factors cannot be ruled out. It should be pointed out that, although we followed them up for 8 years (2), we did not detect severe cognitive impairment in our patients. However, a worsening trend did occur and lower MMSE scores at baseline, even though within age- and schooling-adjusted reference limits, predicted progression of diabetic retinopathy. This study includes a large outpatient population that was carefully followed for a long period of time and used standardized procedures to monitor clinical and psycho-cognitive variables. Limitations are that it was not designed to detect predictors for long term complications, although retinopathy, renal function and cardiovascular risk factors were carefully monitored as part of routine care. In addition, data on adherence to diet and therapy were not collected systematically. Poor adherence may be associated with, among others, polypharmacy (13) and impaired quality of life (14) in type 2 diabetes, both present in most of our patients, and be a risk factor for vascular complications.

In conclusion, end-organ complications of type 2 diabetes may affect different sections of the central nervous system and a test as simple as the MMSE, even when not signalling overtly impaired cognitive function, may hold independent predictive value for the progression of diabetic retinopathy.

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Competing interest. None declared

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Authors Contribution. MT. planned the study, researched the data, contributed to the discussion, drafted and revised the manuscript, and is guarantor of this article, SM. and MS. distributed and analyzed the questionnaires, BA. contributed to the fundus examination, PP. contributed to the discussion, CL. and CF did the statistical analysis, analyzed the data, and revised the manuscript, MP. contributed to the discussion in the study and wrote the manuscript.

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Table 1. Multivariate analysis of the effect of predictors of progression to moderate/more severe DR

Data at baseline	Odds Ratio	CI 95%	p-value
Age	1.03	0.99; 1.07	0.194
Male gender	0.49	0.27; 0.90	**0.021**
Insulin treatment vs not	1.91	1.04; 3.50	**0.036**
HbA1c in pts with no retinopathy at basaline*	1.21	0.95; 1.53	0.122
HbA1c in pts with mild retinopathy at basaline*	1.45	1.13; 1.85	**0.003**
MMSE score	0.90	0.83; 0.99	**0.025**

*we tested for interaction between HbA1c and retinopathy at baseline