Psychoneuroendocrinology 67 (2016) 163–170

Contents lists available at ScienceDirect

Psychoneuroendocrinology

journal homepage: www.elsevier.com/locate/psyneuen

Angiographic evidence of proliferative retinopathy predicts neuropsychiatric morbidity in diabetic patients

Yonatan Serlin[a,b], Tali Shafat[c], Jaime Levy[d], Aaron Winter[e], Marina Shneck[d], Boris Knyazer[d], Yisrael Parmet[f], Hadar Shalev[g], Ehud Ur[h], Alon Friedman[a,b,*]

[a] Department of Physiology and Cell Biology, Zlotowski Center for Neuroscience, Ben-Gurion University of the Negev, Beer-Sheva, Israel
[b] Department of Medical Neuroscience, Faculty of Medicine, Dalhousie University, Halifax, Nova Scotia, Canada
[c] Clinical Research Center, Soroka University Medical Center, Beer-Sheva, Israel
[d] Department of Ophthalmology, Soroka University Medical Center and Faculty of Health Sciences, Ben-Gurion University of the Negev, Beer-Sheva, Israel
[e] Ophthalmology and Visual Sciences, Faculty of Medicine, Dalhousie University, Halifax, Nova Scotia, Canada
[f] Department of Industrial Engineering and Management, Ben-Gurion University of the Negev, Beer-Sheva, Israel
[g] Department of Psychiatry, Soroka University Medical Center, Beer-Sheva, Israel
[h] Division of Endocrinology and Metabolism, University of British Columbia, Vancouver, British Columbia, Canada

ARTICLE INFO

Article history:
Received 13 January 2016
Received in revised form 9 February 2016
Accepted 11 February 2016

Keywords:
Angiography
Blood-brain barrier
Blood-retinal barrier
Diabetic retinopathy
Neuropsychiatry

ABSTRACT

Introduction: Diabetic retinopathy (DR) is a common vasculopathy categorized as either non-proliferative (NPDR) or proliferative (PDR),characterized by dysfunctional blood-retinal barrier (BRB) and diagnosed using fluorescein angiography (FA). Since the BRB is similar in structure and function to the blood-brain barrier (BBB) and BBB dysfunction plays a key role in the pathogenesis of brain disorders, we hypothesized that PDR, the severe form of DR, is likely to mirror BBB damage and to predict a worse neuropsychiatric outcome.

Methods: A retrospective cohort study was conducted among subjects with diabetes ($N = 2982$) with FA-confirmed NPDR ($N = 2606$) or PDR ($N = 376$). Incidence and probability to develop brain pathologies and mortality were investigated in a 10-year follow-up study. We used Kaplan–Meier, Cox and logistic regression analyses to examine association between DR severity and neuropsychiatric morbidity adjusting for confounders.

Results: Patients with PDR had significantly higher rates of all-cause brain pathologies ($P < 0.001$), specifically stroke ($P = 0.005$), epilepsy ($P = 0.006$) and psychosis ($P = 0.024$), and a shorter time to develop any neuropsychiatric event ($P < 0.001$) or death ($P = 0.014$) compared to NPDR. Cox adjusted hazard ratio for developing all-cause brain impairments was higher for PDR (HR = 1.37, 95% CI 1.16–1.61, $P < 0.001$) which was an independent predictor for all-cause brain impairments (OR 1.30, 95% CI 1.04–1.64, $P = 0.022$), epilepsy (OR 2.16, 95% CI 1.05–4.41, $P = 0.035$) and mortality (HR = 1.35, 95% CI 1.06–1.70, $P = 0.014$).

Conclusions: This is the first study to confirm that angiography-proven microvasculopathy identifies patients at high risk for neuropsychiatric morbidity and mortality.

1. Introduction

Diabetes mellitus (DM) is an emergent, common and costly public health problem. In the United States, 9.3% of the population are estimated to have diabetes, including 21 million people diagnosed and 8.1 million undiagnosed (Centers for Disease Control and Prevention, 2014). Vascular complications including endothelial cells dysfunction and proliferation, diminished perfusion, and increased permeability are central to the pathogenesis and clinical manifestations of DM and commonly progress to end organ damage such as retinopathy, nephropathy and neuropathy (Stumvoll et al., 2005). Diabetic retinopathy (DR), manifested by microvascular leakage and occlusion, is an early consequence in the course of DM and eventually develops in the majority of the patients. DR is standardized and graded according to the Early Treatment Diabetic Retinopathy Study (ETDRS) severity scale ("Classification of diabetic retinopathy from fluorescein angiograms. ETDRS report number 11. Early Treatment Diabetic Retinopathy Study Research Group.," 1991). Fluorescein angiography (FA) is the most reliable

* Correspondence to: Departments of Medical Neuroscience and Paediatrics, Faculty of Medicine, Dalhousie University, HaliFax, Nova Scotia, Canada.
E-mail address: alon.friedman@dal.ca (A. Friedman).

http://dx.doi.org/10.1016/j.psyneuen.2016.02.009
0306-4530/

and sensitive imaging method for detecting retinal microangiopathy and vascular leak, and FA imaging enables clinical decision support for treatment considerations and follow-up (Bandello et al., 1999). DR is categorized into two clinical types: non-proliferative and proliferative (NPDR and PDR, respectively). NPDR, the early and less severe stage of DR, is characterized by endothelial injury with dysfunctional blood-retinal brain (BRB) leading to microaneurysms, capillary occlusion, macular edema and result in retinal nonperfusion. PDR, the advanced form of the disease, exhibits abnormal vessel permeability and subsequent severe retinal ischemia with neovascularisation, hemorrhage, fibrosis and/or tractional detachment of the retina. As an extension of the central nervous system (CNS), the retina and the brain share common embryological, anatomical and physiological properties. Accordingly, similar features exist between the BRB and the blood-brain barrier (BBB) (Steuer et al., 2005) and clinical evidence suggest a correlated breakdown of the BRB and BBB under some clinical conditions (Greiner et al., 2015; Ozkan et al., 2014). Accumulating evidence indicate a key role for BBB dysfunction in the pathogenesis of a number of common CNS disorders, including ischemic, hemorrhagic and traumatic brain injuries, vascular dementia, epilepsy and mood disorders (Abbott et al., 2006). The common properties and pathological alterations of small vessels in the brain and retina signify the retina as a 'window' into the brain and suggest that retinal vessel pathology reflects a similar pathology in cerebral vasculature. Retinal pathology has been shown to co-exist in several major CNS disorders including dementia, cognitive dysfunction and brain imaging abnormalities (Cheung et al., 2010; Heringa et al., 2013; Lesage et al., 2009; London et al., 2013). Studies have related damage to the brain vasculature in diabetes as potentially the most significant contributor to psychiatric and cognitive comorbidities (Biessels et al., 2006; Qiu et al., 2014). However, the underlying etiology remains controversial and other mechanisms, including metabolic alterations and inflammatory response have also been suggested (McIntyre et al., 2007). While few studies have reported neurocognitive dysfunction in patients with DR detected by fundus photography alone (Cohen et al., 1997; Crosby-Nwaobi et al., 2013; Ding et al., 2010) there is lack of large scale studies evaluating the association between angiography-proven retinal vasculopathy and CNS morbidity. The purpose of the present study is to investigate whether the severity of retinal vascular pathology, in a well-defined sample of patients with FA-confirmed retinopathy, is associated with increased incidence of CNS complications and mortality and to determine the odds-ratio to develop brain pathology with respect to DR peri-diagnostic period.

2. Methods

2.1. Study subjects and design

We conducted a retrospective cohort study using data collected from the centralized electronic medical records (EMR) database of Clalit Health Services (CHS), the largest health fund in Israel. We analyzed records of 3085 diabetic patients who underwent retinal angiography at a single central eye facility of the southern district of CHS. Of these, 2982 patients were diagnosed with diabetic retinopathy. Eighty-eight cases were diagnosed with type 1 (mean age 46 ± 16 years) and 2894 with type 2 diabetes (mean age 63 ± 11 years). FA images were obtained between January 2005 to December 2012; clinical data (with censoring on death) was documented from a one-year pre-imaging period until August 1, 2014, the end of the follow-up period, in order to track outcomes documented over a contiguous time prior (and close) to the diagnosis of DR. Baseline measures of risk variables were used to study associations of observations taken at one time to subsequent end points. Inclusion criteria for the study were recorded diagnosis of DR and diagnosis of either NPDR or PDR based upon FA imaging. Patients were excluded from the study if they did not fulfill the inclusion criteria. The protocol for this study was approved by the Ethics Committees of Soroka Medical Center and CHS.

2.2. Measures

Data for all subjects were retrieved from CHS EMR central database, integrating administrative and clinical electronic health records, including data from community clinics, hospitals, laboratories, imaging facilities, and pharmacies. Socio-demographic data collected were sex, birth and death dates, country of birth, year of immigration to Israel and marital status. Clinical data included blood pressure monitoring, diagnoses of retinopathy, hypertension, chronic ischemic heart disease (CIHD), congestive heart failure (CHF), atrial fibrillation (AF), peripheral arterial disease (PAD), diabetic nephropathy and neuropsychiatric outcomes including cerebrovascular disease, epilepsy, all-cause dementia, affective and anxiety disorders, parkinsonism, schizophrenia and psychosis. All clinical diagnoses were defined by specified ICD-9 and 10 codes recorded for the first time in the year preceding the FA or until the end of the follow up period. Laboratory data reported from the year prior the FA included HbA_{1c} measurements, lipid profile, albumin/creatinine ratio and the estimated GFR (eGFR), calculated using the Modification of Diet in Renal Disease equation (MDRD). Retinal images were acquired according to a standard clinical protocol as described elsewhere (Bennett, 2001) using a Topcon 50EX camera (Topcon Corporation, Tokyo, Japan; excitation wavelength between 465–490 nm, emission of 520–530 nm). The grades of retinopathy were dichotomized for statistical analysis purposes. All cases were assigned to one of the two DR categories (NPDR vs. PDR) based on FA examinations and interpretation by two fellowship-trained retinal specialists (MS, JL) using OIS WinStation 5000 TM software (Ophthalmic Imaging Systems, Sacramento, CA). Retinopathy severity was determined by the pathological status of the worst affected eye.

2.3. Statistical analysis

Data analysis was performed using SPSS 20.0 (SPSS Inc., Chicago, IL). Continuous variables are expressed as means $\pm$ SD and were tested by independent samples t-tests. Categorical variables are reported as frequencies and percentages and were tested by $\chi 2$ test. The impact of DR status on the 10-year follow-up probability to develop any neuropsychiatric event and on mortality rates was examined by time-to-event variables using Kaplan–Meier survival analysis and evaluated by using Breslow test. Patients who were diagnosed with any event in the year preceding the FA results were considered at time '0' for the purpose of survival calculation. Cox proportional hazards regression models were built to compare the adjusted risk to develop any neuropsychiatric disorder and mortality in PDR versus NPDR patients. Bivariate correlation and univariate logistic regression used to identify association between the outcome and each of the explanatory variables and to detect potential confounders. Clinically relevant factors previously identified in the literature to be associated with DR and brain diseases including cardiovascular comorbidities, renal function, age and gender were tested for adjustment purpose. For each outcome, all significant factors in the univariate regression models were included in the subsequent multivariable model. Adjusted multivariable binary logistic regression analysis was used to examine the odds ratios (OR) and 95% CIs of PDR for developing all-cause neuropsychiatric disorder (grouped) and specific CNS outcomes. The backward-LR variable selection method was used to eliminate the non-significant factors in the final model. For determination