Alzheimer's & Dementia: Translational Research & Clinical Interventions 4 (2018) 165-172

Featured Article

Galectin-3 and incident cognitive impairment in REGARDS, a cohort of blacks and whites

Anand Venkatraman[a], Peter Callas[b], Leslie A. McClure[c], Fred Unverzagt[d], Garima Arora[e], Virginia Howard[f], Virginia G. Wadley[g], Mary Cushman[h], Pankaj Arora[e,i,*]

[a]Department of Neurology, Massachusetts General Hospital/Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA
[b]Department of Mathematics and Statistics, University of Vermont, Burlington, VT, USA
[c]Department of Epidemiology and Biostatistics, Dornsife School of Public Health, Drexel University, Philadelphia, PA, USA
[d]Department of Psychiatry, Indiana University, Indianapolis, IA, USA
[e]Division of Cardiology, Department of Medicine, University of Alabama at Birmingham, Birmingham, AL, USA
[f]Department of Epidemiology, University of Alabama at Birmingham, Birmingham, AL, USA
[g]Department of Medicine, University of Alabama at Birmingham, Birmingham, AL, USA
[h]Department of Medicine, Larner College of Medicine at the University of Vermont, Burlington, VT, USA
[i]Section of Cardiology, Department of Medicine, Birmingham Veterans Affairs Medical Center, Birmingham, AL, USA

Abstract

Introduction: The relationship between serum galectin-3 and incident cognitive impairment was analyzed in the Reasons for Geographic and Racial Differences in Stroke study.

Methods: Baseline galectin-3 was measured in 455 cases of incident cognitive impairment and 546 controls. Galectin-3 was divided into quartiles based on the weighted distribution in the control group, and the first quartile was the referent.

Results: There was an increasing odds of cognitive impairment across quartiles of galectin-3 (odds ratios, 1.00 [0.68–1.46], 1.45 [1.01–2.10], and 1.58 [1.10–2.27] relative to the quartile 1; *P* trend = .003) in an unadjusted model, which persisted after adjusting for age, sex, and race (*P* = .004). Adjustment for cardiovascular risk factors greatly attenuated this association (odds ratios, 0.97 [0.60–1.57], 1.52 [0.94–2.46], and 1.27 [0.76–2.12]; *P* = .15). The association differed by diabetes status (*P* interaction, .007). Among nondiabetics (293 cases, 411 controls), those with galectin-3 in the fourth compared with first quartile had an odds ratio of 1.6 (0.95–2.99; *P* trend, .02). In diabetics, the odds ratio was 0.23 (0.04–1.33).

Discussion: Serum galectin-3 was associated with increased risk of incident cognitive impairment in a large cohort study of blacks and whites but only in nondiabetics.

Keywords: Galectin-3; Cognitive impairment; Biomarkers; Epidemiology; Incidence; Risk factors

1. Background

Cognitive impairment has risen in importance as a public health issue with approximately eight million adults over the age of 71 years in the United States having some form of cognitive impairment [1]. Every year, nearly 12% of patients with milder levels of cognitive impairment progress to dementia [1]. The increasing cost of care for patients with dementia, and the recent increase in trials aimed at controlling the decline of cognitive function in mildly affected individuals, suggests that early detection of those at risk of developing cognitive impairment is of critical importance [2].

Although various factors may contribute to cognitive decline, it is well established that cardiovascular risk factors play a role [3]. In recent years, the carbohydrate-binding

The authors declare they have no financial disclosures and no conflicts of interest.

*Corresponding author. Tel.: 205-996-6630; Fax: 205-975-4720.
E-mail address: parora@uabmc.edu

https://doi.org/10.1016/j.trci.2018.03.006

lectin galectin-3 has received significant attention in the cardiology arena as a circulating biomarker for cardiovascular risk. Galectin-3 can be nuclear or cytoplasmic in location and has been found to have very diverse influences on cellular functioning [4]. Galectin-3 concentration is independently associated with mortality in the general population and in patients with heart failure [5].

Efforts are now underway to investigate the significance of galectin-3 in relation to diseases of the nervous system. Much of the attention has been focused on cerebrovascular diseases [6], but one study found that patients with Alzheimer's disease had higher serum galectin-3 levels than normal controls [7]. Experimental evidence has shown that galectin-3 is involved in inflammatory responses, myelination, and poststroke angiogenesis [8,9].

Given the close relationship between cardiovascular risk factors and cognitive decline [10] and the burgeoning evidence for involvement of galectin-3 in the functioning of the cardiovascular and nervous systems, we hypothesized that galectin-3 was associated with risk of cognitive impairment. We tested our hypothesis by analyzing the relationship between serum galectin-3 levels and incident cognitive impairment in participants in the Reasons for Geographic and Racial Differences in Stroke (REGARDS) cohort.

2. Methods

The REGARDS study is a population-based cohort, investigating racial and geographical disparities in stroke and cognitive disorders [11]. The cohort consists of 30,239 black and white individuals aged 45 years or older who were enrolled between 2003 and 2007, as described previously [11]. The study sampled blacks and residents of the stroke belt (North Carolina, South Carolina, Georgia, Alabama, Mississippi, Tennessee, Arkansas, and Louisiana). A computer-assisted telephone interview was used to obtain demographic and socioeconomic information, medical history, and verbal informed consent. At a subsequent in-home visit, we obtained written informed consent, physical examination results, blood samples, electrocardiogram (ECG), and medications inventory [11]. The study's methods were reviewed and approved by the institutional review boards at each of the study institutions.

2.1. Measurements and definitions

The Six-Item Screener (SIS; three temporal orientation items, and delayed recall of three objects) was used to determine baseline cognitive status. This measure was validated in community and clinical samples including large numbers of black participants [12]. Scores can range between 0 and 6, with four or fewer indicating cognitive impairment. Hypertension was defined as systolic blood pressure $\geq$ 140 mm Hg, diastolic blood pressure $\geq$ 90 mm Hg, or self-reported hypertension with the use of antihypertensive medications. Diabetes was defined as self-reported use of glucose control medications, fasting glucose greater than 126 mg/dL, or nonfasting blood glucose $>$ 200 mg/dL. Dyslipidemia was defined as total cholesterol $>$ 240 mg/dL, low density lipoprotein cholesterol $\geq$ 160 mg/dL, high density lipoprotein $<$ 40 mg/dL, or on medications to treat dyslipidemia. Smoking status was ascertained by asking participants during the telephone interview if they were current cigarette smokers. Alcohol use was determined through participants' self-report. Furthermore, the National Institute on Alcohol Abuse and Alcoholism classification (none, moderate [0–7/week, women; 0–14/week, men], heavy [7+/week, women; 14+/week, men]) was used to distinguish moderate and heavy drinking. Physical activity was assessed by asking about how frequently the participants engaged in intense physical activity per week (1–3 times/week or four or more times/week). We calculated the estimated glomerular filtration rate using the Chronic Kidney Disease Epidemiology Collaboration formula, with chronic kidney disease defined as estimated glomerular filtration rate $<$ 60 mL/min/1.73 m^2 [13]. Left ventricular hypertrophy was classified using a centrally read ECG. Congestive heart failure was defined based on self-report on orthopnea or paroxysmal nocturnal dyspnea. We used self-report or presence on ECG to determine atrial fibrillation. Prebaseline heart disease was defined by self-reported bypass, myocardial infarction, angioplasty or stenting, or evidence of myocardial infarction on ECG. Prebaseline stroke was defined by self-report of a diagnosis by a physician. Medical records of suspected stroke after baseline were centrally adjudicated as described previously [14].

2.2. Longitudinal cognitive assessment

Participants are contacted every six months to ascertain potential stroke events and cognitive function. Starting in 2006, a three-test battery was performed every 2 years. This included Word List Learning (WLL) and Word List Recall and Semantic fluency (animals), all from the Consortium to Establish a Registry for Alzheimer's Disease [15]. The Word List Learning score is the number of words recalled on a 10-item, three-trial word list learning task (range could be from 0 to 30). The Word List Recall score is the number of words recalled after a filled delay (range could be from 0 to 10). Semantic fluency is the number of animals that could be named in 60 seconds. These tests were administered in a staggered fashion for ease of administration by telephone. We supervised all testing with quality control monitoring.

2.3. Case-control study design

We used a nested case-control study to select a subset of REGARDS participants for galectin-3 measurements and to provide results that would approximate measurement of galectin-3 in the entire cohort. Methods have been reported elsewhere [16]. We excluded participants with prevalent stroke (n = 1930), cognitive impairment at the baseline