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Diabetes, aging, and cognitive decline

Christopher M. Ryan *

Department of Psychiatry, Western Psychiatric Institute & Clinic, University of Pittsburgh School of Medicine, 3811 O'Hara Street, Pittsburgh, PA 15213, USA

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Abstract

Type 1 diabetes is associated with cognitive changes in children and adults, but the extent to which cognition declines with increasing age, and increasing duration of diabetes, remains poorly understood. This cross-sectional study assessed neuropsychological performance on 200 diabetic and 175 nondiabetic adults, 18–64 years of age, stratified into five age bands. Similar age-related cognitive declines were seen on measures of problem-solving, learning and memory, and psychomotor speed, but it was only on the latter measure that diabetic and nondiabetic subjects differed significantly. The best predictor of psychomotor slowing was the presence of clinically significant biomedical complications, particularly proliferative retinopathy, peripheral neuropathy, and peripheral vascular disease (PVD). It now appears that psychomotor slowing is the fundamental cognitive deficit associated with diabetes mellitus; why other cognitive skills are relatively unaffected remains poorly understood.

Keywords: Diabetes; Cognitive function

1. Introduction

Mild cognitive dysfunction is not at all uncommon in individuals with insulin-dependent diabetes. Children [32] and adults [4] with type 1 diabetes manifest cognitive changes on measures of intelligence, psychomotor efficiency, cognitive flexibility, and rapid information-processing. A growing body of literature has suggested that diabetes-related cognitive dysfunction is largely a consequence of changes within the central nervous system (CNS) that are secondary to chronic hyperglycemia [3,16,21]. Common to diabetes and to degenerative dementias like Alzheimer's disease are cerebrovascular changes [15,20,46], free-radical-mediated oxidative stress [2,31], formation of advanced glycation end products [43,44], and possibly, impairments in cerebral insulin signaling systems [13].

Studies of healthy nondiabetic individuals drawn from the community at large have demonstrated that cognitive decline is an almost inevitable part of the normal aging process. These changes may begin remarkably early in adulthood, with cognitive decline evident by 35 years of age on measures of abstract reasoning, memory, and mental speed [40]. If the putative pathophysiological mechanisms underlying cognitive dysfunction are similar in both diabetes and aging, one might expect to find synergistic effects. That is, with increasing disease duration as well as with increasing age, diabetic adults might show an acceleration in the rate and magnitude of cognitive decline, as compared to their healthy peers.

2. Cognitive dysfunction, diabetes and aging: a cross-sectional analysis

To estimate the extent to which cognitive function decreases over time, as the duration of diabetes increases and as the individual ages, we analyzed neuropsychological and biomedical data collected on 200 adults with type 1 diabetes, and 175 nondiabetic comparison subjects.

2.1. Subjects

Diabetic subjects were recruited from the Pittsburgh epidemiology of diabetes complications study population [26],

* Tel.: +1 412 246 5392; fax: +1 412 246 5425.
E-mail address: ryancm@upmc.edu.

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which is comprised of a childhood-onset (<17 years) cohort of type 1 diabetic individuals seen within 1 year of diagnosis at Children's Hospital of Pittsburgh. Nondiabetic subjects were recruited by asking each diabetic patient to name a spouse, sibling, significant other, or close friend. Individuals were excluded if they had a current or past history of chronic alcohol or drug abuse, a head injury with a loss of consciousness that exceeded 30 min, or a current psychiatric disorder. At the time of this assessment, subjects ranged in age from 18 to 64 years (mean ± S.D., 38.4 ± 9.6), and the duration of diabetes ranged from 6 to 57 years (mean ± S.D., 28.9 ± 8.4).

2.2. Cognitive performance

A comprehensive battery of cognitive tests was completed by each subject. The cross-sectional analyses described herein are based on six measures representative of three broad cognitive domains. Problem-solving was assessed with the Block Design subtest (total raw score) from the Wechsler adult intelligence scale revised (WAIS-R) [45], and by the Wisconsin Card Sorting Test (number of perseverative errors) [11]. Learning and memory was assessed with the Verbal Paired Associate Learning Test (total correct across four study/test trials) [37], and by the Four Word Short-term Memory Test (total correct across the 5, 15, and 30 s retention intervals), a task that provides a measure of verbal working memory proficiency [23]. Psychomotor efficiency was measured with the Grooved Pegboard [19] (average time from dominant and nondominant hands to insert key-shaped pegs into a board with 25 'keyholes') and with the Digit Vigilance Test [18] (total time to scan two pages of numbers for a designated target). Detailed descriptions of each test can be found elsewhere [34].

2.3. Biomedical variables

Diabetic subjects received a detailed medical examination with appropriate laboratory tests to assess the presence of microvascular and macrovascular complications and comorbid disorders. Nondiabetic comparison subjects completed a similar but abbreviated medical examination. Measures included: stable glycosylated hemoglobin (HbA_1), blood pressure, retinopathy (stereoscopic color fundus photography), nephropathy (timed urine samples), distal symmetric polyneuropathy (DSP; clinical neurological evaluation), peripheral vascular disease (PVD; ankle/arm blood pressure readings), and coronary artery disease (CAD; diagnosed angina or coronary artery stenosis confirmed by angiography) [36].

2.4. Analyses

Based on the ages of diabetic subjects, the sample was stratified into age quintiles; diabetes duration [mean ± S.D.] in years for each age band is in brackets: (18–30 [19.3 ± 3.7]; 31–34 [24.1 ± 4.0]; 35–39 [27.6 ± 5.0]; 40–44 [32.3 ± 4.4]; 45–64 [40.1 ± 5.1]). To facilitate comparisons of the different tests, raw scores for each were converted into *Z*-scores (mean ± S.D., 0 ± 1), using the values from the nondiabetic comparison subjects; lower values reflect worse performance. A two-way analysis of variance (group × age quintile) was conducted for each cognitive outcome variable.

2.5. Cognitive results

On both problem-solving measures, performance worsened with increasing age (Block Design score: $p < .0001$; Wisconsin Perseveration score: $p < .007$), but there was no effect of group, nor a group × age interaction. That is, diabetic subjects declined as well, but were no worse than their nondiabetic peers. Essentially the same pattern of results was seen on measures of verbal learning, and working memory. Age effects were much weaker here, and were evident only on the Paired Associate Learning Test ($p = .01$). In contrast, as shown in Fig. 1, there was a large and robust statistical difference between the diabetic and nondiabetic subjects on measures of psychomotor efficiency. Not only was there a pronounced effect of age ($p < .001$), but there was a marked effect of group, with the diabetic subjects taking consistently longer to complete the Digit Vigilance Test ($p < .0001$) and the Grooved Pegboard Test ($p < .0001$). These between-group differences emerge relatively early in the adult lifespan and are evident by the age of 30 on both tests ($p < .05$). Performance continues to deteriorate dramatically after the age of 34, particularly on the Grooved Pegboard Test (age × group interaction: $p = .05$).

2.6. Predictors of psychomotor decline

An exploratory analysis of possible biomedical predictors of age-related psychomotor slowing was undertaken by conducting a multiple regression analysis using the Grooved Pegboard score as the dependent variable. Predictors included

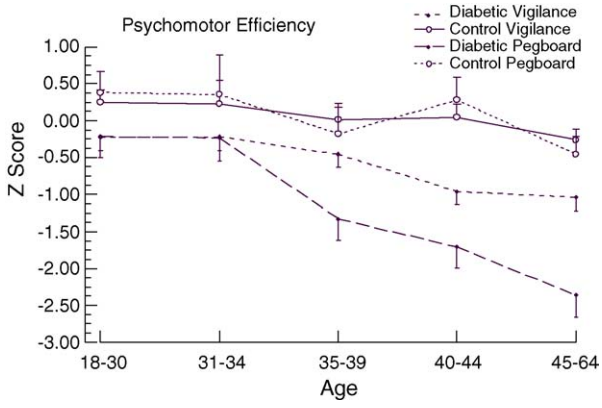

Fig. 1. Performance (mean ± S.E.M.) of diabetic and nondiabetic adults, stratified into five age bands, on two measures of psychomotor efficiency: the mean time taken by the dominant and nondominant hand to complete the Grooved Pegboard, and the total time taken to complete two pages of the Digit Vigilance Test.