Biophysical Correlates of Cognition Among Depressed and Nondepressed Type 2 Diabetic Patients

VIRGINIA ELDERKIN-THOMPSON, PHD[1]
GERHARD HELLEMANN, PHD[2]
RAKESH K. GUPTA, MD[3]
ANAND KUMAR, MD[1]

OBJECTIVE — Caudate magnetization transfer (MT) ratios have indicated an abnormality in the macromolecular protein pool of diabetic patients. This study examined the relationship between MT ratios of the caudate and cognitive performance.

RESEARCH DESIGN AND METHODS — Diabetic patients, diabetic and depressed patients, and healthy comparison subjects completed magnetic resonance imaging and a neuropsychological battery. Magnetization transfer ratios of caudate and three comparison regions were computed. The neuropsychological battery was aggregated into a global index of cognitive function and correlated with MT ratios.

RESULTS — MT ratios of the caudate correlated with cognitive performance, and the correlations were stronger among diabetic patients than healthy control subjects. Comorbid depression increased the strength of the correlation compared with diabetes alone. Comparison regions showed no evidence of a diabetes effect on cognition.

CONCLUSIONS — One mechanism precipitating cognitive loss during diabetes appears to be associated with cellular changes occurring in the macromolecular protein pool of the caudate.

Diabetes Care 32:48–50, 2009

Magnetization transfer (MT) is a magnetic resonance imaging (MRI)-related approach used to study the biological integrity of myelin and axonal density in the white matter and a composite index of macromolecular proteins in gray matter regions. A recent report from our laboratory using MT documented a decline in the saturated signal intensity of macromolecular proteins in the head of the caudate in diabetic patients that is exacerbated in patients with concurrent depression (1). Consequently, diabetes is associated with some loss of cellular integrity in the caudate due to macromolecular protein dysfunction.

This study examined the relationship between cognitive functioning of diabetic patients and MT ratios from caudate and three comparison regions: putamen, dorsolateral periventricular white matter, and anterior cingulate. The rich and diverse communication pathways (2,3) passing through the caudate are important for several aspects of cognition, so we hypothesized that global cognitive function would be associated with caudate MT ratios. The other comparison regions provided information on the specificity of the cognition-caudate association.

RESEARCH DESIGN AND METHODS

— An ongoing study on diabetes and depression is being conducted at UCLA Medical Center. Depressed and nondepressed patients were under care provided at UCLA clinics affiliated with departments of internal medicine and endocrinology. Subjects were screened with the Structured Clinical Interview for DSM-IV (SCID) (4), the Mini Mental Status Examination (MMSE), the American Heart Association's Stroke Risk Prediction Chart (CVRF) (5), and the Cumulative Illness Rating Scale (CIRS) (6). Participants completed an electrocardiogram and a standard battery of laboratory tests. The study protocol was approved by the UCLA Institutional Review Board. Please see Elderkin-Thompson et al. (7) and Kumar et al. (8) for complete procedures.

Neuropsychological battery

The neuropsychological battery included tests of working memory (Letter-Number Sequences), language (Controlled Oral Word Association, or FAS), simple attention and processing (Stroop 1 and 2, Trailmaking A, Digit Symbol Substitution), procedural learning (Wisconsin Card Sorting Test), executive function (Matrix Reasoning, Trailmaking B, Stroop Interference), visuospatial conceptualization (Block Designs), and declarative learning and recall (California Verbal Learning Test, trials 1–5, short and delayed recall). Cronbach's $\alpha = 0.90$ for the composite global scale indicated good reliability.

Methods

MRI was performed with a 1.5 Tesla scanner (Signa, Lx echospeed plus 9.1; General Electric Medical System, Milwaukee, WI) using a transmit/receive quadrature head coil. Imaging was performed in an axial plane using fast-spin echo T2 and MT T1 weighted sequences. Details on MRI acquisition and MT methods have been previously reported (9,10). In MT imaging, an off-resonance radio frequency pulse is used to minimize the exchange of protons between bound water (bound to macromolecular proteins) and free water compartments in the brain (11,12). The resulting image is a subtraction of the image with the RF pulse from the original one without the pulse.

Statistical plan

Demographic and clinical variables were analyzed with ANOVAs and post hoc con-

From the [1]Semel Institute for Neuroscience and Human Behavior, Geriatric Division, University of California, Los Angeles, Los Angeles, California; the [2]Semel Institute for Neuroscience and Human Behavior, Biostats Core, University of California, Los Angeles, Los Angeles, California; and the [3]Sanjay Gandhi Institute of Post Graduate Medical Education and Research, Lucknow, India.
Corresponding author: Virginia Elderkin-Thompson, velderkin@mednet.ucla.edu.
Received 14 May 2008 and accepted 19 September 2008.
Published ahead of print at http://care.diabetesjournals.org on 3 October 2008. DOI: 10.2337/dc08-0899.

Table 1—*Between-group differences of demographic and clinical characteristics*

	Depressed diabetic	Diabetic comparison	Healthy comparison	*F* (df = 2,56)*	*P*
n	13	18	28		
Age	59.46 ± 11.41	62.00 ± 9.47	55.04 ± 11.00	2.47	0.09
Education	14.85 ± 2.08	15.22 ± 2.67	16.43 ± 3.18	1.79	0.18
CIRS (total symptoms)	7.23 ± 2.62†	6.78 ± 3.80‡	2.57 ± 2.20	17.47	<0.01
SF-36 (general health)	42.30 ± 25.46†§	73.06 ± 16.73‡	85.54 ± 12.42	27.84	<0.01
CVRF (age adjusted)	11.08 ± 3.08†	9.72 ± 3.14‡	3.36 ± 3.73	28.48	<0.01
Diabetes age of onset	49.18 ± 16.27	52.23 ± 10.08	NA	0.38	0.54
Diabetes duration (months)	140.73 ± 114.23	115.76 ± 95.99	NA	0.39	0.54
Depression age of onset	53.91 ± 12.70	NA	NA		
Depression duration	84.18 ± 66.13	NA	NA		
Ham-D	20.45 ± 4.32	NA	NA	NA	NA
A1C	7.46 ± 1.53†§	6.70 ± 1.09‡	5.40 ± 0.43	19.58	<0.01
Mini Mental Status Examination	27.38 ± 2.90†	28.61 ± 1.78	29.07 ± 1.15	3.71	0.03
Global cognition (*z* score)	−0.46 ± 0.74†§	−0.13 ± 0.58‡	0.29 ± 0.53	7.44	<0.01
MT ratio					
Bilateral caudate	29.06 ± 2.56†§	32.26 ± 2.08‡	35.14 ± 1.05	31.41 [2,55]	<0.001
Bilateral putamen	33.57 ± 2.23	33.82 ± 1.38	35.08 ± 0.98	2.42 [2,55]	0.10
Frontal periventricular	43.58 ± 1.41	43.85 ± 1.65	44.29 ± 1.73	0.13 [2,55]	0.88
White matter					
Anterior cingulate	25.06 ± 5.01	26.63 ± 3.87	27.99 ± 3.58	0.38 [2,54]	0.69
				χ^2	*P*
Sex				χ^2 [2] = 1.49	0.47
Male	2 (15)	6 (33)	6 (21)		
Female	11 (85)	12 (67)	22 (79)		
Ethnicity				χ^2 [8] = 9.90	0.27
African American	2 (15)	4 (22)	3 (11)		
Latino	2 (15)	2 (11)	1 (4)		
Asian	3 (23)	3 (17)	3 (11)		
Caucasian	5 (38)	7 (39)	21 (75)		
Other	1 (8)	2 (11)	0		

Data are means ± SD or *n* (%). *df of 2,56 applied to all analyses unless otherwise stated. Ham-D, Hamilton Rating Scale for Depression; SF-36 General Health, RAND SF-36 Short Form General Health subtest. †Difference between depressed diabetic patients and healthy comparison subjects, $P < 0.01$. ‡Difference between nondepressed diabetic group and healthy comparison subjects, $P < 0.05$. §Difference between nondepressed diabetic group and depressed diabetic group, $P < 0.05$.

trast tests (Table 1). MT ratios across groups were compared using CIRS as a covariate because diagnostic groups differed in their symptom counts. CIRS, CVRF, and short-form (SF)-36 were highly intercorrelated, so CIRS was selected as the most representative of general health status. Cognitive scores were standardized, with higher scores representing better performance and tested for homogeneity (Cronbachs $\alpha = 0.89$). The global cognitive scale was correlated with MT ratios after CIRS adjustment. Brain regions that correlated with the cognitive index were examined by plotting the MT ratio by the cognitive index.

RESULTS — Diagnostic groups differed on global cognition, with both diabetic groups performing significantly below the comparison group and depressed performing significantly below nondepressed diabetic patients. MT ratios from the caudate differed across diagnostic groups and formed the same step decline of means observed in the cognitive index.

Correlations

MT ratios of caudate and putamen correlated with the cognitive index after adjustment for CIRS total symptom count (caudate, r [59] = 0.36, $P = 0.006$; putamen, r [59] = 0.44, $P = 0.001$). Correlations remained significant after Bonferroni's correction ($\alpha = 0.0125$). Correlation coefficients for the remaining regions were small to trivial.

In the subgroup analysis, healthy comparison individuals did not demonstrate a relationship between cognition and caudate MT ratios (r [28] = 0.24, $P = 0.23$). Diabetic patients as a group did show a relationship (r [31] = 0.37, $P = 0.04$), but there was no significant difference between the correlations of control subjects and patients (Fisher's z difference = 0.52, $P = 0.60$). When the diabetic group was further subdivided into depressed and nondepressed patients, only the depressed diabetic subjects showed an association (r [13] = 0.56, $P = 0.05$), but this also was not significantly different from healthy comparison subjects (z difference = 1.04, $P = 0.30$).

In the putamen, control subjects demonstrated no linear relationship between MT ratios and cognition (r [28] = 0.08, $P = 0.70$). Diabetic patients showed a relationship (r [31] = 0.59, $P = 0.001$), which was significantly different from healthy control subjects (Fisher's z difference = 2.17, $P = 0.03$). In the patient subgroups, both nondepressed and depressed diabetic patients showed an association (r [18] = 0.50, $P = 0.04$; r [13] = 0.66, $P = 0.01$, respectively), although neither correlation was significantly dif-

ferent from the healthy comparison group ($z = 1.44$, $P = 0.15$; $z = 1.90$, $P > 0.05$).

Scatterplots (not provided) demonstrated the different patterns of association for the two regions. In the caudate, data points of diagnostic groups showed some segregation with three apparent clusters of scores, consistent with significant mean differences. The healthy comparison group was clustered primarily above the MT and cognition means, depressed diabetic subjects were largely below both means, and nondepressed diabetic subjects were grouped at the means. In the putamen, the data points from the groups were interspersed with no group mean differences.

CONCLUSIONS — As hypothesized, global cognitive performance correlated with caudate MT ratios. The finding that the MT-cognition correlation was stronger among patients then among healthy comparison subjects, and stronger among depressed diabetic patients than nondepressed diabetic patients, suggests a threshold pattern in which the MT effect is modest but notable when only diabetes is present, but it becomes exacerbated when both diabetes and depression are present. MT ratios from the putamen correlated with global cognition, but the means did not differ between groups, so there was no obvious disease effect. Although interpretation of low MT ratios in white and gray matter are not yet understood, physiological abnormalities in cell membranes and proteins together with neuronal and synaptic loss are currently posited as explanations for differences.

A methodological caution results from the small sample size and low power of the analysis. Differences between groups may become significant with a larger sample, and the role of the putamen deserves further study. In conclusion, our results, although preliminary, suggest that one mechanism underlying mild cognitive decline in diabetes may lie in abnormalities of the protein biochemistry of the caudate.

Acknowledgments — Research grant support was provided by the National Institutes of Mental Health (RO1 MH 63764 to A.K., principal investigator) and the General Clinical Research Center at UCLA (MO1 RR00865).

No potential conflicts of interest relevant to this article were reported.

References

1. Kumar A: Subcortical physiological abnormalities in type 2 diabetes detected using magnetization transfer (Abstract). Berlin, Germany, International Society for Magnetic Resonance Imaging (ISMRM), May 2007
2. Schmahamann JD, Pandya DN: White matter pathways in early neuroscience. In *Fiber Pathways of the Brain*. New York, Oxford University Press, 2006, p. 7–37
3. Schmahmann JD, Pandya DN: Approach to the study of the fiber tracts. In *Fiber Pathways of the Brain*. New York, Oxford University Press, 2006, p. 41–81
4. First MB, Spitzer RL, Gibbon M, Williams J: *Structured Clinical Interview for DSM-IV Axis I Disorders*. New York, State Psychiatric Institute, 1996
5. American Heart Association: *Stroke Risk Factor Prediction Chart* (derived from the Framingham Heart Study sponsored by the National Heart, Lung and Blood Institute of the National Institutes of Health). Dallas, TX, American Heart Association, 1990
6. Linn BJ, Linn BW, Gurel L: Cumulative Illness Rating Scale. *J Am Geriatr Soc* 16: 622–626, 1968
7. Elderkin-Thompson V, Ballmaier M, Hellemann G, Pham D, Lavretsky H, Kumar A: Daily functioning and prefrontal brain morphology in healthy and depressed community-dwelling elderly. *Am J Geriatr Psychiatry* 16:633–642, 2008
8. Kumar A, Haroon E, Darwin C, Pham D, Ajilore O, Rodriguez G, Mintz J: Gray matter prefrontal changes in type 2 diabetes detected using MRI. *J Magn Reson Imaging* 27:14–19, 2008
9. Kumar A, Gupta RC, Alger J, Wyckoff N, Hwang S: Biophysical changes in normal-appearing white matter and subcortical nuclei in late-life major depression detected using magnetization transfer. *Psychiatry Res* 130:131–140, 2004
10. Kumar A, Gupta R, Thomas A, Ajilore O, Hellemann G: Subcortical biophysical abnormalities in patients diagnosed with type 2 diabetes and depression. *Arch Gen Psychiatry*. In press
11. Eng J, Ceckler TL, Balaban RS: Quantitative 1H magnetization transfer imaging in vivo. *Magn Reson Med* 17:304–314, 1991
12. Henkelman RM, Stanisz GJ, Graham SJ: Magnetization transfer in MRI: a review. *NMR Biomed* 14:57–64, 2001