Cerebral Perfusion and Aortic Stiffness Are Independent Predictors of White Matter Brain Atrophy in Type 1 Diabetic Patients Assessed With Magnetic Resonance Imaging

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OBJECTIVE—To identify vascular mechanisms of brain atrophy in type 1 diabetes mellitus (DM) patients by investigating the relationship between brain volumes and cerebral perfusion and aortic stiffness using magnetic resonance imaging (MRI).

RESEARCH DESIGN AND METHODS—Approval from the local institutional review board was obtained, and patients gave informed consent. Fifty-one type 1 DM patients (30 men; mean age 44 ± 11 years; mean DM duration 23 ± 12 years) and 34 age- and sex-matched healthy control subjects were prospectively enrolled. Exclusion criteria comprised hypertension, stroke, aortic disease, and standard MRI contraindications. White matter (WM) and gray matter (GM) brain volumes, total cerebral blood flow (tCBF), total brain perfusion, and aortic pulse wave velocity (PWV) were assessed using MRI. Multivariable linear regression analysis was used for statistics, with covariates age, sex, mean arterial pressure, BMI, smoking, heart rate, DM duration, and HbA_{1c}.

RESULTS—Both WM and GM brain volumes were decreased in type 1 DM patients compared with control subjects (WM $P = 0.04$; respective GM $P = 0.03$). Total brain perfusion was increased in type 1 DM compared with control subjects ($\beta = -0.219$, $P < 0.05$). Total CBF and aortic PWV predicted WM brain volume ($\beta = 0.352$, $P = 0.024$ for tCBF; respective $\beta = -0.458$, $P = 0.016$ for aortic PWV) in type 1 DM. Age was the independent predictor of GM brain volume ($\beta = -0.695$, $P < 0.001$).

CONCLUSIONS—Type 1 DM patients without hypertension showed WM and GM volume loss compared with control subjects concomitant with a relative increased brain perfusion. Total CBF and stiffness of the aorta independently predicted WM brain atrophy in type 1 DM. Only age predicted GM brain atrophy.

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In type 1 diabetes mellitus (DM) patients, early development of brain atrophy (1,2), which may affect cognitive functioning (3), has been demonstrated. Multiple pathophysiological mechanisms like repeated hypoglycemic episodes (4), chronic hyperglycemia (5), and alterations in insulin metabolism and associated insulin use (6) are suggested to be involved in the development of cerebral complications in type 1 DM. Although cerebral atrophy is common in neurodegenerative processes, decreased brain volumes have been associated with vascular risk factors (3,7), suggesting vascular mechanisms contributing to the development of brain atrophy. Indeed, the hyperglycemic state of DM induces structural changes and endothelial dysfunction of the macro- and microvasculature (8). Impaired cerebrovascular reactivity in type 1 DM has been demonstrated recently (9), and cerebral perfusion abnormalities have been found in type 1 DM patients in earlier studies (10). The cerebral circulation plays an important role in the maintenance of neuronal cell integrity, and therewith potentially in the development of brain atrophy.

Furthermore, arterial stiffening has shown to occur in type 1 DM, being an independent predictor of cardiovascular outcome (11). The elastic aorta is the predominant site of pathologic arterial stiffening. Aortic stiffening increases pulse wave velocity (PWV) and pulse pressure (PP), placing considerable pulsatile stress on the peripheral circulation. The brain is a high flow organ and therewith particularly susceptible to pulsatile stress. Therefore, it is conceivable that aortic stiffness is contributing to the pathogenesis of brain atrophy in type 1 DM.

Although the associations between type 1 DM and cerebral perfusion or arterial stiffening have been described, their relationship with brain volumes in this patient group, to investigate potential vascular mechanisms causing brain atrophy, has not been assessed until now.

Quantitative measurements of brain volumes can be accurately evaluated on scans obtained by magnetic resonance imaging (MRI) (12). MRI using phase-contrast is a reliable method for estimating total cerebral blood flow (tCBF) (13) as well as for evaluating aortic stiffness by means of PWV (14).

Accordingly, the purpose of the current study was to identify potential underlying vascular mechanisms of brain atrophy in type 1 DM patients by investigating the relationship between brain volumes and cerebral perfusion

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and aortic stiffness in this patient group using MRI.

RESEARCH DESIGN AND METHODS

Study participants

Between February 2008 and January 2010, a total of 51 consecutive type 1 DM patients from the local outpatient clinic of the Leiden University Medical Center and 34 age- and sex-matched healthy control subjects recruited by advertisement in local newspapers participated in the study. Healthy control subjects did not have a history or clinical evidence of DM, hypertension, or cardiovascular disease. Exclusion criteria for all participants included a clinical history or diagnosis of hypertension according to the guidelines of the European Society of Cardiology, stroke, aortic valve stenosis, or insufficiency as evaluated by means of cardiac auscultation and velocity-encoded MRI, Marfan syndrome, and standard MRI contraindications like claustrophobia, pacemaker, and metal implantations.

Information about type 1 DM and healthy control characteristics was obtained by standardized interviews and physical and laboratory examinations. Type 1 DM duration was estimated as the time passed between the reported age of diagnosis and the MRI examination. BMI was calculated from body length and mass at the time of MRI. Blood pressure and heart rate were measured after MRI using a semiautomated sphygmomanometer (Dinamap, Critikon, Tampa, FL, validated to ANSI/AAMI SP10 criteria). PP was defined as the difference between systolic and diastolic blood pressure. Mean arterial pressure (MAP) was calculated by adding diastolic blood pressure to one-third of the PP. Smoking was defined as nonsmoker or a current smoker. Retinopathy was recognized on fundoscopy. Monofilament testing was used to diagnose peripheral neuropathies. Microalbuminuria was defined as 30–300 mg albumin/24-h urine collection or microalbumuria/creatinine ratio >2.5 mg/mmol for men or >3.5 mg/mmol for women. HbA_{1c} in type 1 DM, fasting glucose in healthy control subjects, high-density lipoprotein (HDL), total cholesterol, triglycerides, and creatinine were furthermore determined.

The study was approved by the local medical ethics committee and conducted according to the principles in the Declaration of Helsinki. All study participants signed informed consent.

MRI protocol

All brain examinations were performed on a 3.0-Tesla MRI (Achieva; Philips Medical Systems, Best, the Netherlands). Aortic imaging was performed using 1.5-Tesla MRI (NT 15 Gyroscan Intera; Philips Medical Systems, Best, the Netherlands).

Brain MRI consisted of a three-dimensional T1 sequence for brain volume assessment and a two-dimensional phase contrast scan at the level of the skull base for flow measurements in the internal carotid arteries and basilar artery.

For the evaluation of white matter (WM) and gray matter (GM) brain volumes, the three-dimensional T1 image (repetition time [TR] 9.8 ms, echo time [TE] 4.6 ms, flip angle [FA] 8°, field of view [FOV] 224 mm, 192 × 152 acquisition matrix, 256 × 256 reconstruction matrix, slice thickness 1.2 mm, 120 slices, no slice gap) was obtained. Software package SIENAX automatically segments brain from nonbrain matter; calculates white, gray, and total brain volume; and applies a normalization factor to correct for skull size (12). To avoid confounding brain volume measurements because not all scans included the full brain, the SIENAX analyses were restricted to a prespecified interval along the *z*-axis, ranging from 75 to −52 mm in standard MNI152 space. SIENAX is part of the FMRIB Software Library (FSL). All SIENAX analyses were performed using FSL version 2.6.

Total CBF was calculated from the electrocardiographic-triggered two-dimensional phase contrast images (TR 13 ms, TE 8.3 ms, FA 10°, FOV 150 mm, 128 × 88 acquisition matrix, 256 × 256 reconstruction matrix, slice thickness 5 mm, no slice gap, velocity sensitivity 140 cm/s) using the software package FLOW (Leiden University Medical Center, Leiden, the Netherlands). An experienced researcher drew manual regions of interest closely around the vessel lumen of the internal carotid arteries and the basilar artery (S.v.E., 3 years of experience in neuroradiology). The flow through the three arteries was summed and multiplied by the individual's heart rate during MR scanning to calculate the tCBF (in mL/min). In three subjects (two type 1 DM patients, one healthy control) tCBF could not be obtained due to incorrect positioning of the phase-contrast imaging plane. Total brain perfusion (in mL/min per 100 mL) was assessed by dividing tCBF (in mL/min) by each individual's total brain volume (in mL) and multiplying the obtained result by 100.

For the evaluation of aortic stiffness, aortic PWV was determined using a previously described protocol (14). In short, a scout view of the aorta was performed. Next, a velocity encoded image perpendicular to the ascending aorta at the level of the pulmonary trunk was assessed. This resulted in through-plane flow measurements of the ascending and proximal descending aorta at those levels. Linear regression between 20 and 80% of the range between diastolic flow and peak systolic flow determines the line following the upstroke. Time point of intersection between the upstroke and the baseline of the flow curve was considered being the arrival time of the foot of the pulse wave. Aortic PWV was subsequently calculated for the aorta as $\Delta x/\Delta t$, where Δx is the aortic path length between the two measurement sites measured in the aortic scout view and Δt is the time delay between the arrivals of the foot of the pulse wave at the respective measurement sites. Data were analyzed using MASS and FLOW (Leiden University Medical Center) by two observers (S.v.E. and A.B., both 4 years of experience in cardiac MRI) supervised by a senior researcher (J.W., 15 years of experience in cardiac MRI).

Statistical analysis

Data are expressed as mean ± SD. To compare clinical characteristics between type 1 DM and healthy control subjects independent samples *t* test for continuous variables and χ^2 test for dichotomous variables were used. Kolmogorov-Smirnov test showed that aortic PWV was nonnormally distributed ($P < 0.001$). Therefore, a log transformation of aortic PWV values was used in the analyses. To compare MR findings between type 1 DM and healthy control subjects, linear regression analysis with covariates age, sex, and MAP was applied.

In type 1 DM multivariable linear regression analysis was performed to study the association between brain volumes and tCBF and aortic PWV, independent of potential confounders defined as age, sex, MAP, BMI, smoking, heart rate, DM duration, and HbA_{1c}. *P* value <0.05 was considered statistically significant. We used SPSS for Windows (version 16.0; SPSS, Chicago, IL) for statistical analysis.

RESULTS—The characteristics of the study population are described in Table 1. Fifty-one type 1 DM patients (30 men,

Table 1—*Clinical characteristics and MRI parameters of type 1 DM patients and healthy control subjects*

	Type 1 DM patients	Healthy control subjects	*P* value
n	51	34	—
Characteristics			
Age (years)	44 ± 11	46 ± 14	0.46
Men, *n* (%)	30 (59%)	17 (50%)	0.42
BMI (kg/m^2)	25.0 ± 3.2	26.2 ± 3.9	0.18
Blood pressure (mmHg)			
Systolic	126 ± 18	128 ± 15	0.62
Diastolic	74 ± 10	80 ± 11	<0.01*
PP (mmHg)	52 ± 13	47 ± 13	0.11
MAP (mmHg)	91 ± 11	96 ± 11	0.04*
Heart rate (bpm)	65 ± 10	61 ± 10	0.05
Current smoker, *n* (%)	8 (16%)	2 (6%)	0.17
Retinopathy, no/minimal background/laser treated	16/31/4		
Peripheral neuropathy, *n* (%)	7 (14%)		
Microalbuminuria, *n* (%)	4 (8%)		
Laboratory markers			
HbA_{1c} (%)	7.6 ± 1.0	NA	NA
Fasting glucose level	NA	4.9 ± 0.6	NA
Cholesterol (mmol/L)			
HDL	1.7 ± 0.5	1.6 ± 0.4	0.34
Total	4.7 ± 0.9	5.3 ± 1.2	0.01*
Triglycerides (mmol/L)	1.1 ± 0.6	1.4 ± 0.7	0.04*
Creatinine (μmol/L)	74 ± 11	77 ± 17	0.32
MRI findings			
Aortic PWV (m/s)	5.3 (4.7–6.1)	5.7 (4.6–7.6)	0.21
tCBF (mL/min)	466 ± 131	424 ± 111	0.27
Total brain perfusion (mL/min per 100 mL brain tissue)	41.3 ± 11.0	36.4 ± 9.0	<0.05†
Brain volume (mL)			
WM	567 ± 72	583 ± 70	0.04†
GM	565 ± 59	584 ± 54	0.03†
Total	1,132 ± 124	1,167 ± 117	<0.01†

*Significantly different between groups using independent samples *t* test, $P < 0.05$. †Significantly different between groups, in multivariable linear regression analysis correcting for age, sex, and MAP, $P < 0.05$.

21 women, mean age 44 ± 11 years, mean type 1 DM duration 23 ± 12 years) and 34 healthy control subjects were included. All type 1 DM patients were on insulin treatment. Type 1 DM and healthy control subjects were comparable in age, sex, BMI, systolic blood pressure, PP, heart rate, current smokers, HDL cholesterol, and creatinine. Type 1 DM patients showed lower diastolic blood pressure ($P < 0.01$), lower total cholesterol ($P = 0.01$), and lower triglyceride levels ($P = 0.04$). Twelve type 1 DM patients used statins, whereas none of the healthy volunteers did. One out of the 51 type 1 DM patients used an ACE inhibitor and an angiotensin II antagonist for the presence of microalbuminuria. None of the type 1 DM patients were on β-blocker use. None of the volunteers used antihypertensive medication.

WM brain volumes and GM brain volumes, normalized for skull size, were decreased in type 1 DM patients compared with healthy control subjects ($P = 0.04$ for WM; respective $P = 0.03$ for GM brain volume). Total brain perfusion was significantly increased in type 1 DM compared with healthy control subjects presenting with similar systolic blood pressures and corrected for age, sex, and MAP ($\beta = -0.219$, $P < 0.05$). Aortic PWV values were in the normal range in the type 1 DM patient and healthy control subjects ($P = 0.21$).

Table 2 shows the results of multivariable linear regression analyses to assess independent predictors for WM and GM brain volume in type 1 DM. Both tCBF and aortic PWV were independent predictors of WM brain volume ($\beta = 0.352$, $P = 0.024$ for tCBF; respective $\beta = -0.458$, $P = 0.016$ for aortic PWV) in type 1 DM patients in a model including covariates age, sex, MAP, BMI, smoking, heart rate, DM duration, and HbA_{1c}. In a similar multivariable linear regression model for GM brain volume, age was a significant predictor ($\beta = -0.695$, $P < 0.001$) and tCBF and aortic PWV were not. Both total CBF and aortic PWV did not independently predict WM or GM brain volumes in healthy control subjects.

CONCLUSIONS—The purpose of the current study was to assess the possible association between brain volumes and cerebral perfusion and aortic stiffness in type 1 DM patients without hypertension by using MRI. The main findings of our study were: *1*) type 1 DM patients showed WM and GM volume loss compared with healthy control subjects concomitant with a relative increased brain perfusion; *2*) total CBF and stiffness of the aorta independently predicted WM brain atrophy; and *3*) age was the only independent predictor of GM brain atrophy, whereas tCBF and aortic PWV were not.

Our findings of cortical and subcortical atrophy in type 1 DM are in line with previous studies reporting mild cerebral atrophy in type 1 DM compared with control subjects (1,2). Furthermore, we found concomitant hyperperfusion of the brain. Impaired echo Doppler measured cerebrovascular reactivity has been described before in type 1 DM in accordance with our findings (9,15). The Framingham heart study reported the exposure of cardiovascular disease risk factors, like DM, associated with high resting arterial flow and impaired vasoreactivity (16). The vasodilatory effect of persistent hyperinsulinemia was mentioned as a possible mechanism of the high resting arterial blood flow (17).

Furthermore, in our current study tCBF and aortic stiffness were both predictors of WM brain atrophy. Recently, two large cohort studies were the first to investigate and report associations between CBF and brain volumes (18,19). An elevation in CBF, particularly in the presence of factors that stiffen the aorta, may allow additional pulsatility to penetrate into and damage the microcirculation with subsequent cerebral tissue loss (20,21). A similar mechanism is a well-known phenomenon in the kidneys; renal

Table 2—*Results of multivariable linear regression analyses performed in type 1 DM patients to assess independent predictors of WM and, respectively, GM brain volumes*

	Brain volume			
	WM		GM	
	β	*P* value	β	*P* value
Age (years)	0.13	0.56	−0.70	<0.001
Men (*n* = 30)	−0.27	0.06	0.14	0.21
MAP (mmHg)	−0.04	0.80	−0.10	0.45
BMI (kg/m^2)	0.20	0.15	−0.03	0.77
Smoking, yes (*n* = 8)	0.06	0.68	0.12	0.28
DM duration (years)	−0.18	0.35	0.02	0.91
HbA_{1c} (%)	−0.04	0.83	0.23	0.08
Aortic PWV (m/s)	−0.46	0.02	0.07	0.62
tCBF (mL/min)	0.35	0.02	0.11	0.36

hyperperfusion is present in the earliest stages of type 1 DM and considered to contribute to renal injury and the progression to clinical nephropathy (22). It has been suggested that the brain and the kidneys, both high flow organs with low impedance vascular beds, present a common and unique vascular reactivity mechanism on blood pressure and flow fluctuations.

We found aortic stiffness as an independent predictor of WM brain atrophy. To the best of our knowledge, no studies investigated this relationship before. Measurements of aortic PWV represent propagation speed of the PP, which is influenced by both functional and structural changes of the arterial vessel wall. An earlier study found a positive correlation between MR parameters of brain atrophy and wall thickness of the internal carotid artery as well as a diagnosis of DM and the current use of insulin in community-dwelling elderly (3), which is in congruence with our findings. Because vascular resistance in the brain is very low, pulsations can extend well into the microvascular cerebral bed. It is remarkable that the aortic PWV was still in the normal range without statistical significant difference as compared with that in healthy control subjects. We speculate that the brain of type 1 DM patients may be susceptible to relative small changes in aortic PWV, even when PWV appears to be relative normal. Moreover, aortic stiffness may be a marker of arterial function and inflammatory processes manifesting in cerebral arteries and arterioles.

Of note, the association between aortic PWV and WM brain volume was found independent of tCBF, suggesting two separate vascular mechanisms operating on WM brain atrophy.

The associations between WM brain volumes and tCBF as well as aortic PWV could not be shown for GM brain volumes. It is known that the blood flow in the GM is substantially higher to the amount of blood flow in the WM because of high metabolic activity in the GM (23). Subtle fluctuation in arterial blood flow or function may therefore spare GM brain volume, in contrast with the vulnerable end-arterioles penetrating the WM. An earlier study suggested that persistent hyperglycemia and acute severe hypoglycemic events have an impact on early subtle alterations in GM structure in type 1 DM patients (24). In our study age was the only and strong predictor of GM brain atrophy, confirming the theory of accelerated brain aging in DM.

This study has some limitations. Our study design does not allow revealing the exact (complex) mechanisms by which increased cerebral blood flow and normal values of aortic PWV affect WM brain volume in type 1 DM. Both a direct detrimental pulsatile effect on the cerebral microcirculation as well as impaired vascular compensatory mechanisms during conditions such as hypoglycemia, hypotension, and hypoxia may be involved in tissue loss of the vulnerable diabetic brain (6). Second, involvement of autonomic neuropathy can be assumed for the presence of cerebral hyperperfusion according to the (nonsignificant) higher heart rate in our type 1 DM patients. Future studies are needed to explore these mechanisms.

Our results may have important implications. First, our study results reveal further insight into the pathophysiology of brain atrophy in type 1 DM. Our findings suggest two separate vascular mechanisms, namely tCBF and aortic stiffness, being involved in WM brain atrophy in type 1 DM patients, independent of glucose regulation. Second, our findings may have prognostic implications. Assessment of aortic PWV may have prognostic implications, even when values fall into the normal range, possibly due to increased brain susceptibility in DM patients. Furthermore, the arterial system is known to stiffen with older age and high blood pressure (25). When patients with type 1 DM become older or develop hypertension, increased aortic stiffening may occur with subsequent adverse changes in WM brain volumes. On the other hand, methods likely to detect subtle changes in the brain are essential for evaluating the effects of type 1 DM on the brain since the gradual progress of cerebral changes may make them difficult to detect until years after onset of type 1 DM. Earlier detection of brain structural changes may increase the likelihood that treatment interventions can slow down the progression of these impairments. However, longitudinal studies are required to confirm our results and to investigate the clinical implications of our findings.

In conclusion, type 1 DM patients without hypertension showed WM and GM volume loss compared with healthy control subjects concomitant with a relative increased brain perfusion. Total CBF and stiffness of the aorta independently predicted WM brain atrophy in type 1 DM patients. Only age predicted GM brain atrophy. Future prospective studies are needed to assess the prognostic and clinical implications of these initial observations.

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