Cardiovascular magnetic resonance imaging techniques in hypertension and diabetes

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Chapter 06

Cerebral Perfusion and Aortic Stiffness Are Independent Predictors of White Matter Brain Atrophy in Type-1 Diabetes Mellitus Patients, Assessed with MRI

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Abstract

Purpose

To identify vascular mechanisms of brain atrophy in type-1 diabetes mellitus (DM1) patients by investigating the relationship between brain volumes and cerebral perfusion and aortic stiffness using magnetic resonance imaging (MRI).

Materials and Methods

Approval from the local institutional review board was obtained and patients gave informed consent. Fifty-one DM1 patients (30 men; mean age 44 ± 11 years; mean DM duration 23 ± 12 years) and 34 age and gender matched healthy controls, were prospectively enrolled. Exclusion criteria comprised hypertension, stroke, aortic disease and standard MRI contra-indications. White matter (WM) and grey 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 co-variates age, gender, mean arterial pressure, body mass index, smoking, heart rate, DM duration and HbA1c.

Results

Both WM and GM brain volumes were decreased in DM1 patients compared to controls (WM: $p = 0.04$; GM: $p = 0.03$). Total brain perfusion was increased in DM1 compared to controls ($\beta = -0.219$, $p < 0.05$). Total CBF and aortic PWV predicted WM brain volume (tCBF $\beta = 0.352$, $p = 0.024$; aortic PWV $\beta = -0.458$, $p = 0.016$) in DM1. Age was the independent predictor of GM brain volume ($\beta = -0.695$, $p < 0.001$).

Conclusion

DM1 patients without hypertension showed WM and GM volume loss compared to controls concomitant with a relative increased brain perfusion. Total CBF and stiffness of the aorta independently predicted WM brain atrophy in DM1. Age only was predicting GM brain atrophy.

Introduction

In type-1 diabetes mellitus (DM1) patients, early development of brain atrophy (1,2) which may affect cognitive functioning (3,4) has been demonstrated. Multiple pathophysiological mechanisms like repeated hypoglycemic episodes (5), chronic hyperglycemia (6) and alterations in insulin metabolism and associated insulin use (7) are suggested to be involved in the development of cerebral complications in DM1. Although cerebral atrophy is common in neurodegenerative processes, decreased brain volumes have been associated with vascular risk factors (3,8), 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 (9). Impaired cerebrovascular reactivity in DM1 has been demonstrated recently (10) and cerebral perfusion abnormalities have been found in DM1 patients in earlier studies (11,12). 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 DM1, being an independent predictor of cardiovascular outcome (13). 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 DM1.

Although the associations between DM1 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 so far.

Quantitative measurements of brain volumes can be accurately evaluated on scans obtained by magnetic resonance imaging (MRI) (14). MRI using phase-contrast is a reliable method for estimating total cerebral blood flow (tCBF) (15) as well as for evaluating aortic stiffness by means of PWV (16).

Accordingly, the purpose of the current study was to identify potential underlying vascular mechanisms of brain atrophy in DM1 patients by investigating the relationship between brain volumes and cerebral perfusion and aortic stiffness in this patient group using MRI.

Materials and Methods

Study participants

Between February 2008 and January 2010, in total 51 consecutive DM1 patients from the local outpatient clinic of the Leiden University Medical Center and 34 age and gender matched healthy controls recruited by advertisement in local newspapers participated in

the study. Healthy controls 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 contra-indications like claustrophobia, pacemaker and metal implantations.

Information about DM1 and healthy control characteristics was obtained by standardized interviews and physical and laboratory examinations. DM1 duration was estimated as the time passed between the reported age of diagnosis and the MRI examination. Body mass index (BMI) was calculated from body length and mass at the time of MRI. Blood pressure (RR) and heart rate were measured after MRI using a semi-automated sphygmomanometer (Dinamap, Critikon, Tampa, Florida, USA, validated to ANSI/AAMI SP10 criteria). Pulse pressure was defined as the difference between systolic and diastolic RR. Mean arterial pressure (MAP) was calculated by adding diastolic RR to one-third of the PP. Smoking was defined as non-smoker 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/24h urine collection or microalbumuria/creatinine ratio > 2.5 mg/mmol for men or >3.5 mg/mmol for women. Glycated hemoglobin (HbA1c) in DM1, fasting glucose in healthy controls, 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 3-dimensional T1 sequence for brain volume assessment and a 2-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 grey matter (GM) brain volumes the 3D T1 image (repetition time (TR) 9.8 msec, echo time (TE) 4.6 msec, flip angle (FA) 8˚, field of view (FOV) 224 mm, 192 x 152 acquisition matrix, 256 x 256 reconstruction matrix, slice thickness 1.2 mm, 120 slices, no slice gap) was obtained. Software package SIENAX automatically segments brain from non-brain matter, calculates white, grey and total brain volume, and applies a normalization factor to correct for skull size (14). To avoid confounding brain volume measurements because not all scans included the full brain, the SIENAX analyses were restricted to a pre-specified 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 2D phase contrast images (TR 13 msec, TE 8.3 msec, FA 10˚, FOV 150 mm, 128 x 88 acquisition matrix, 256 x 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 year 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 DM1 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 (ml/min) by each individual's total brain volume (ml) and multiplying the obtained result by 100.

For the evaluation of aortic stiffness, aortic PWV was determined using a previously described protocol (16). 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, Leiden, the Netherlands) by two observers (S.v.E. and A.B., both 4 years of experience in cardiac MRI) supervised by a senior researcher (J.J.M.W., 15 years of experience in cardiac MRI).

Statistical Analysis

Data are expressed as mean ± standard deviation (sd). To compare clinical characteristics between DM1 and healthy controls independent samples t-test for continuous variables and Chi-Square 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 DM1 and healthy controls linear regression analysis with covariates age, gender and MAP was applied.

In DM1 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, gender, MAP, BMI, smoking, heart rate, DM duration and HbA1c. A p-value < 0.05 was considered statistically significant. We used SPSS for Windows (version 16.0; SPSS, Chicago, Illinois, USA) for statistical analysis.

Results

The characteristics of the study population are described in Table 1. Fifty-one DM1 patients (30 male, 21 female, mean age 44 ± 11 years, mean DM1 duration 23 ± 12 years) and 34 healthy controls were included. All DM1 patients were on insulin treatment. DM1 and healthy controls were comparable in age, gender, BMI, systolic RR, PP, heart rate, current smokers, HDL-cholesterol and creatinine. DM1 patients showed lower diastolic RR ($p < 0.01$), lower total cholesterol ($p = 0.01$) and lower triglyceride levels ($p = 0.04$). Twelve DM1 patients used statins, whereas none of the healthy volunteers did. One out of the fifty-one DM1 patients used an ACE-inhibitor and an angiotensin II-antagonist for the presence of microalbuminuria. None of the DM1 patients were on beta-blocker use. None of the volunteers used antihypertensive medication.

WM brain volumes and GM brain volumes, normalized for skull size, were decreased in DM1 patients compared to healthy controls ($p = 0.04$ for WM; resp. $p = 0.03$ for GM brain volume). Total brain perfusion was significantly increased in DM1 compared to healthy controls presenting with similar systolic blood pressures and corrected for age, gender and mean arterial pressure (MAP) (Beta regression coefficient (β) = -0.219, $p < 0.05$). Aortic PWV values were in the normal range in DM1 patients and healthy controls ($p = 0.21$).

Table 2 shows the results of multivariable linear regression analyses to assess independent predictors for WM and GM brain volume in DM1. Both tCBF and aortic PWV were independent predictors of WM brain volume ($\beta = 0.352$, $p = 0.024$ for tCBF, resp. $\beta = -0.458$, $p = 0.016$ for aortic PWV) in DM1 patients in a model including co-variates age, gender, MAP, BMI, smoking, heart rate, DM duration and HbA1c. 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 controls.

Discussion

The purpose of the current study was to assess the possible association between brain volumes and cerebral perfusion and aortic stiffness in DM1 patients without hypertension by

Table 1. Clinical characteristics and MRI parameters of DM1 patients and healthy controls

	Type 1 DM patients (n=51)	*Healthy controls (n=34)*	*p-value*
Characteristics			
Age, years	44 ± 11	46 ± 14	0.46
Male gender, n (%)	30 (59%)	17 (50%)	0.42
Body mass index, kg/m^2	25.0 ± 3.2	26.2 ± 3.9	0.18
Systolic RR, mmHg	126 ±18	128 ± 15	0.62
Diastolic RR, mmHg	74 ± 10	80 ± 11	<0.01*
Pulse pressure, mmHg	52 ± 13	47 ± 13	0.11
Mean arterial pressure, mmHg	91 ± 11	96 ± 11	0.04*
Heart rate, beats/min	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			
HbA1c, %	7.6 ± 1.0	na	na
Fasting glucose level	na	4.9 ± 0.6	na
HDL-cholesterol, mmol/l	1.7 ± 0.5	1.6 ± 0.4	0.34
Total cholesterol, mmol/l	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
Total cerebral blood flow, 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†
White matter brain volume, ml	567 ± 72	583 ± 70	0.04†
Grey matter brain volume, ml	565 ± 59	584 ± 54	0.03†
Total brain volume, ml	1132 ± 124	1167 ± 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, gender and MAP, $p<0.05$

Abbreviations: DM: diabetes mellitus; RR: blood pressure; HbA1c: glycated hemoglobin, HDL: high density lipoprotein; PWV: pulse wave velocity

using MRI. The main findings of our study were: 1. DM1 patients showed WM and GM volume loss compared to healthy controls concomitant with a relative increased brain perfusion; 2. Total CBF and stiffness of the aorta independently predicted WM brain atrophy; 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 DM1 are in line with previous studies reporting mild cerebral atrophy in DM1 compared to controls (1,2). Furthermore, we found concomitant hyperperfusion of the brain. Impaired echo Doppler measured cerebrovascular reactivity has been described before in DM1 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

Table 2. Results of multivariable linear regression analyses performed in DM1 patients to assess independent predictors of WM and respectively GM brain volumes

	WM brain volume		*GM brain volume*	
	Beta	*p-value*	*Beta*	*p-value*
Age, years	0.13	0.56	-0.70	<0.001
Gender, male (n=30)	-0.27	0.06	0.14	0.21
Mean arterial pressure, mmHg	-0.04	0.80	-0.10	0.45
Body mass index, 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
HbA1c, %	-0.04	0.83	0.23	0.08
Aortic PWV, m/s	-0.46	0.02	0.07	0.62
Total cerebral blood flow, ml/min	0.35	0.02	0.11	0.36

Abbreviations: WM: white matter; GM: grey matter; DM: diabetes mellitus; HbA1c: glycated hemoglobin; PWV: pulse wave velocity

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 hyperperfusion is present in the earliest stages of DM1 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 pulse pressure 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 to that in healthy controls. We speculate that the brain of DM1 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 to 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 DM1 patients (24). In our study age was the only and strong predictor of GM brain atrophy, confirming the theory of accelerated brain ageing 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 pulse wave velocity effect white matter brain volume in DM1. Both a direct detrimental pulsatile effect on the cerebral microcirculation as well as impaired vascular compensatory mechanisms during conditions as hypoglycaemia, 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 (non-significant) higher heart rate in our DM1 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 DM1. Our findings suggest two separate vascular mechanisms, namely tCBF and aortic stiffness, being involved in WM brain atrophy in DM1 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 DM1 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 DM1 on the brain since the gradual progress of cerebral changes may make them difficult to detect until years after onset of DM1. Earlier detection of brain structural changes may increase the likelihood that treatment interventions can slow down the progression of these impairment. However, longitudinal studies are required to confirm our results and to investigate the clinical implications of our findings.

In conclusion, DM1 patients without hypertension showed WM and GM volume loss compared to healthy controls concomitant with a relative increased brain perfusion. Total CBF and stiffness of the aorta independently predicted WM brain atrophy in DM1 patients. Age only predicted GM brain atrophy. Future prospective studies are needed to assess the prognostic and clinical implications of these initial observations.

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