Clinical and MRI Features of Cerebral Small-Vessel Disease in Type 1 Diabetes

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Clinical and magnetic resonance imaging features of cerebral small vessel disease in type 1 diabetes

Short running title: Cerebral small vessel disease in diabetes

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Abstract

Objective: To assess the prevalence of cerebral small vessel disease (SVD) in type 1 diabetes compared with healthy controls, and to characterize the diabetes-related factors associated with SVD.

Research Design and Methods: The Finnish Diabetic Nephropathy Study, cross-sectional design; 191 participants with type 1 diabetes, median age 40.0 (interquartile range 33.0-45.1) years, and 30 healthy, age- and sex-matched controls. All participants underwent clinical investigation and brain MRIs, assessed for cerebral SVD.

Results: Cerebral SVD was more common in participants with type 1 diabetes than in healthy controls: any marker 35% vs. 10% (P=0.005), cerebral microbleeds (CMBs) 24% vs. 3.3% (P=0.008), white matter hyperintensities 17% vs. 6.7% (P=0.182), lacunes 2.1% vs. 0% (P=1.000). Presence of CMBs was independently associated with systolic blood pressure, odds ratio 1.03 (95% confidence interval 1.00-1.05), P=0.035.

Conclusions: Cerebral SVD, CMBs in particular, is more common in young persons with type 1 diabetes compared with healthy controls.

Type 1 diabetes is associated with a five-fold increased risk of stroke (1), with cerebral small vessel disease (SVD) as the most common etiology (2). Cerebral SVD in type 1 diabetes, however, remains scarcely investigated, and is challenging to study *in vivo per se*, due to the size of affected vasculature (3), and instead, MRI signs of SVD are studied. In this study, we aimed to assess the prevalence of cerebral SVD in type 1 diabetes compared with healthy controls, and characterize diabetes-related variables associated with SVD in stroke-free persons with type 1 diabetes.

Research Design and Methods

All study participants are part of the Finnish Diabetic Nephropathy Study (4). Participants attending the Helsinki University Hospital (HUH) study center were consecutively recruited, and underwent brain MRI as part of their study visit. In 2011-2017, we studied 191 participants with type 1 diabetes. Inclusion criteria were age 18-50 years and type 1 diabetes onset <40 years. Exclusion criteria were presence of end-stage renal disease, clinical signs of cerebrovascular disease, or contraindications for MRI. We studied 30 healthy age- and sex-matched controls with mean fasting glucose 4.4 ± 0.4 mmol/l.

The study protocol was approved by the Ethics Committee of the HUH, and the study was carried out in accordance with the Declaration of Helsinki. Each participant signed a written informed consent.

All participants underwent a clinical study visit (4). Brain MRI was performed with a 3.0 Tesla scanner (Achieva, Philips, Best, The Netherlands) at the Helsinki Medical Imaging Center, HUH, and included T1, T2, FLAIR, SWI, T2*, DWI, T1 MPRAGE, and MRA TOF. An experienced neuroradiologist (J.M.) assessed the images, and repeated the assessment three times per participant, for markers of SVD (5; 6): presence of cerebral microbleeds (CMBs), cortical superficial siderosis, white-matter hyperintensities (WMHs) (Fazekas scale used, with

category ≥1 considered to be significant burden), or lacunes. The neuroradiologist was blinded to clinical data, but not to whether the participant had diabetes.

We analyzed parametric variables with t-tests, and present results as means with standard deviation, and non-parametric variables with Mann-Whitney U tests presented as medians with interquartile range. We analyzed categorical variables with χ^2-test or Fisher's Exact Test when appropriate. We performed logistic regression to determine independent associations with cerebral SVD, and present results as odds ratio (OR) with 95% confidence intervals. Statistical significance was $P<0.05$. All analyses were performed with IBM SPSS Statistics 22 software (IBM Inc., Armonk, NY).

Results

Clinical characteristics and MRI findings of the 191 participants with type 1 diabetes and the 30 age- and sex-matched controls appear in Table 1.Of the 67 participants with type 1 diabetes and SVD, 32 (48%) had only CMBs, 20 (30%) only WMHs, 11 (16%) both CMBs and WMHs, two (3%) both CMBs and lacunes, and two (3%) both WMHs and lacunes (Supplemental Figure S1).

Participants with type 1 diabetes and CMBs had more often presence of albuminuria (27% vs. 12%, P=0.021), antihypertensive medication (49% vs. 32%, P=0.033), and higher systolic blood pressure (135 ± 17 vs. 129 ± 13 mmHg, P=0.009) (Supplemental Table S1). Only systolic blood pressure was independently associated with CMBs: OR for one mmHg increment 1.03 (95% confidence interval 1.00-1.05), P=0.035. Eight participants had more than ten CMBs (range 10 to 105). These eight participants were older than 38 years, 50% had albuminuria, 75% history of retinal photocoagulation, 88% hypertension, 25% were on aspirin therapy, and none used anticoagulant therapy.

Participants with WMHs (Fazekas ≥1) were significantly older [44.9 (40.8-47.6) vs. 38.6 (32.5-44.2) years, P<0.001] and had a higher systolic blood pressure (137 ± 15 vs. 129 ± 14 mmHg, P=0.005) (Supplemental Table S2). Only age was independently associated with WMHs, OR for age per one year increment 1.11 (1.04-1.19), P=0.003.

Conclusions

Cerebral SVD is more common in participants with type 1 diabetes, than healthy controls. Especially CMBs are more prevalent, and are independently associated with hypertension. Our results indicate that cerebral SVD starts early in type 1 diabetes, but is not explained solely by diabetes-related vascular risk factors or the generalized microvascular disease that takes place in diabetes (7).

There are only small-scale studies on cerebral SVD, especially CMBs, in type 1 diabetes. Compared to the present study, one study with similar diabetes characteristics as in the present study, but lacking a control population, showed a higher prevalence of WMHs, with more than half of the participants affected, but similar prevalence of lacunes, and lower prevalence of CMBs (8). In another study, including 67 participants with type 1 diabetes and 33 controls, there was no difference in WMH prevalence, but a higher prevalence of CMBs in participants with type 1 diabetes and retinopathy compared with controls (9).

In the present study, CMBs were not associated with retinopathy, but on the other hand, associated with albuminuria, a strong marker of generalized microvascular disease. In addition, CMBs were independently associated with higher systolic blood pressure. Hypertension has also been associated with CMBs in the general population (10), but other studies show conflicting results (11). In type 1 diabetes, albuminuria and systolic blood pressure independently increase the risk for both ischemic and hemorrhagic stroke (12).

Cerebral amyloid angiopathy and hypertensive vasculopathy are the two most common pathogenetic processes underlying cerebral SVD. Both diseases cause microaneurysms, vessel disruption, microthrombosis, and arteriolosclerosis, leading to permeable and disrupted microvasculature (3). In the present study, CMBs were mainly observed in the lobar brain regions, which has been associated with cerebral amyloid angiopathy – a condition generally affecting the elderly, whereas CMBs in the deeper parts associate with hypertensive vasculopathy (3). It is, however, unlikely that the lobar predominance of CMBs in our younger participants would indicate cerebral amyloid angiopathy. The majority of those with several CMBs had hypertension and presence of microvascular diabetic complications, indicating a more generalized vasculopathy, although CMBs were not associated with other vascular risk factors, such as diabetes duration, BMI, glycemic control, or smoking. Lobar CMBs mostly lie on the proximal course of medullary end-arteries supplying the white matter of the brain. We hypothesize that CMBs represent similar pathology to that observed in diabetic retinopathy, e.g. rupture of a microaneurysm (13). Chronic inflammation or some factor associated solely with type 1 diabetes itself, e.g. autoimmunity, could also contribute to the increase in CMBs observed in our study.

We showed a trend towards more WMHs in type 1 diabetes. Previous studies in type 1 diabetes show conflicting results, with some reporting more WMHs in type 1 diabetes (14) and others not (9; 15). Most WMHs in our study were classified as Fazekas category one, and only four participants had lacunes, and all of them with type 1 diabetes.

The strengths of our study include standardized enrollment of participants, age- and sex-matched healthy controls, and standardized imaging and assessment. Although our study is the largest on type 1 diabetes and SVD prevalence to date, we did not have sufficient power to detect minor differences between the groups. The cross-sectional study setting also limits the interpretation of causal relationships.

We conclude that cerebral SVD is more common in type 1 diabetes than healthy controls. Future studies will focus on longitudinal development of SVD in type 1 diabetes and the associations with brain health and cognition.

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L.M.T., S.S., D.G., R.L., C.F., P.S., S.H.-H., T.T., O.S., J.P., J.M., and P.-H.G. contributed to the study design, acquisition of data, as well as the interpretation of data. L.M.T. and S.S. had the main responsibility for analyzing the data and writing the first draft of the paper. D.G., R.L., C.F., P.S., S.H.-H., T.T., O.S., J.P., J.M., and P.-H.G. critically revised the manuscript. P.-H.G., is the guarantor of this work and, as such, had full access to all the data in the study, and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Conflict of interest statement. P.S. has received lecture honoraria from Bayer and Santen. T.T. is an advisory board member of Boehringer Ingelheim, Bayer, Pfizer, and Lumosa Therapeutics, and has received speaker honoraria from the University of Donau (Austria), and the Finnish Neurological Association. P-H.G. has received lecture honoraria from AstraZeneca, Boehringer Ingelheim, Eli Lilly, Elo Water, Genzyme, Medscape, MSD, Novartis, Novo Nordisk, and Sanofi, and he is an advisory board member of AbbVie, Boehringer Ingelheim, Eli Lilly, Janssen, Medscape, MSD, Novartis, Novo Nordisk, and Sanofi. The other authors declare no conflict of interest.

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Table 1. Clinical characteristics and MRI findings in participants with type 1 diabetes and controls matched for age and sex.

	Type 1 diabetes	**Controls**	**P-value**
N	191	30	
Clinical characteristics			
Sex, N (%) women	101 (53)	17 (57)	0.699
Age, years	40.0 (33.0-45.1)	38.4 (31.4-43.2)	0.443
Diabetes duration, years	21.7 (18.3-30.9)	-	-
Body mass index, kg/m^2	26.7 ± 4.2	24.5 ± 3.2	0.002
Systolic blood pressure, mmHg	130 ± 14	121 ± 11	0.001
Diastolic blood pressure, mmHg	77 (71-82)	76 (74-85)	0.387
HbA_{1c}, % (mmol/mol)	8.2 ± 1.1 (66 ± 12)	5.1 ± 0.2 (33 ± 2)	<0.001
Creatinine, µmol/l	68 (61-79)	74 (68-81)	0.067
Total Cholesterol, mmol/l	4.4 (4.0-4.9)	4.6 (4.2-5.4)	0.178
LDL Cholesterol, mmol/l	2.4 (2.0-2.9)	2.6 (2.3-3.3)	0.017
HDL Cholesterol, mmol/l	1.50 (1.25-1.80)	1.46 (1.26-1.68)	0.362
Triglycerides, mmol/l	0.90 (0.68-1.38)	0.84 (0.69-1.26)	0.398
Antihypertensive medication, N (%)	68 (36)	0	<0.001
Statin therapy, N (%)	42 (22)	0	0.002
Aspirin therapy, N (%)	15 (7.9)	0	0.232
Albuminuria, N (%)	30 (16)	0	0.018
Retinal photocoagulation, N (%)	42 (22)	0	0.002
Coronary heart disease, N (%)	1 (0.5)	0	1.000
Current smoking, N (%)	15 (7.9)	5 (17)	0.118
Other autoimmune disease, N (%)	63 (33)	6 (20)	0.149
MRI findings			
Cerebral small vessel disease, N (%)	67 (35)	3 (10)	0.005
CMBs, N (%)	45 (24)	1 (3.3)	0.008
Number of CMBs			1.000
1, N (% of those with CMBs)	27 (60)	1 (100)	
2, N (% of those with CMBs)	6 (13)	0	
≥3, N (% of those with CMBs)	12 (27)	0	
Topography of CMBs			
Strictly lobar, N (% of those with CMBs)	38 (84)	1 (50)	0.315
Strictly deep or infratentorial, N (% of those with CMBs)	3 (6.7)	1 (50)	0.165
Mixed, N (% of those with CMBs)	4 (8.9)	0	1.000
Cortical superficial siderosis, N (%)	0	0	-
Any WMH, N (%)	44 (23)	2 (6.7)	0.051
Fazekas Category 1, N (%)	33 (17)	2 (6.7)	0.182
Lacunes, N (%)	4 (2.1)	0	1.000
Stenosis of carotid arteries, N (%)	2 (1.0)	0	1.000
Incidental findings, N (%)	20 (10)	4 (13)	0.751
Unremarkable MRI scan, N (%)	107 (56)	24 (80)	0.013

Data are N-values (percentages), median (interquartile range), or mean ± standard deviation. eGFR= estimated glomerular filtration rate, MRI= magnetic resonance imaging, CMBs= cerebral microbleeds, WMH= white matter hyperintensity.