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Published in:
Brain Research

DOI (link to publication from Publisher):
10.1016/j.brainres.2024.149288

Publication date:
2025

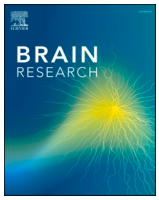
Document Version
Publisher's PDF, also known as Version of record

Brain Research 1846 (2025) 149288

Contents lists available at ScienceDirect

Brain Research

journal homepage: www.elsevier.com/locate/brainres



Research paper

Quantification of white matter hyperintensities in type 1 diabetes and its relation to neuropathy and clinical characteristics

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ARTICLE INFO

Keywords:
Central nervous system
Diabetic neuropathy
Magnetic resonance imaging
Peripheral nervous system
White matter hyperintensities

ABSTRACT

Aims: The aims were to quantify periventricular and deep white matter hyperintensities (WMHs) in adults with type 1 diabetes with different neuropathic phenotypes and to correlate WMH measurements to explanatory factors in diabetes.
Methods: WMH measurements were obtained from brain magnetic resonance imaging of 56 adults with type 1 diabetes in subgroups including painful diabetic peripheral neuropathy (DPN), painless DPN, without DPN and 20 healthy controls using Fazekas scale and automatic segmentation analysis.
Results: No differences in Fazekas assessed WMHs were found (individuals with periventricular lesions: diabetes 66 % vs. controls 40 %, $p = 0.063$, deep lesions: diabetes 52 % vs. controls 50 %, $p = 1.0$). Using automatic detection, there were no significant differences in count of periventricular ($p = 0.30$) or deep ($p = 0.31$) WMHs. Higher periventricular lesion burden was present in diabetes compared with controls (0.21 % vs. 0.06 %, $p = 0.048$), which was associated with more severe DPN, increased age, decreased cognitive function, and reduced volumetric and metabolic brain measures (all $p < 0.05$).
Conclusions: Our findings indicate increased burden of periventricular WMHs in diabetes which were associated to DPN severity and measurements reflecting neurodegeneration. Deep WMHs, often considered as chronic ischemic, were not significantly different. Mechanisms reflecting neurodegeneration and accelerated brain aging could be an overlooked aspect of peripheral and central neuropathy.

1. Introduction

Diabetic neuropathy affects both the peripheral and the central nervous system. Over the last decades, evidence of brain alterations in type 1 diabetes has been established (Seaquist, 2015; Van Harten et al., 2006a), but it is still not fully understood if brain alterations are specific to diabetes as a systemic disease and/or to more specific diabetes-related complications, i.e. neuropathy. Therefore, a better understanding of associations between brain alterations in type 1 diabetes and disease characteristics is needed. Focusing on structural brain alterations, there have been several studies investigating gray matter loss in adults with type 1 diabetes (Croosu et al., 2022; Hansen et al., 2022; Selvarajah et al., 2014), but other studies also describe alterations in white matter such as global white matter volume loss (Selvarajah et al., 2019), altered white matter microstructure assessed by diffusion tensor imaging (DTI) (Alotaibi et al., 2021; Frokjaer et al., 2013; Muthulingam et al., 2022) and leukoaraiosis assessed as increased burden of white matter hyperintensities (WMHs) (Van Harten et al., 2006b). WMHs are lesions that are considered to reflect damage to small vessels (Debette and Markus, 2010) and investigation of WMHs can provide insights into pathologic

Abbreviations: WMH, White matter hyperintensity; DPN, Diabetic peripheral neuropathy; DTI, Diffusion tensor imaging; FLAIR, Fluid attenuated inversion recovery; NAA/cre, N-acetylaspartate/creatine; MEDON, Methods of Early Detection of diabetic peripheral Neuropathy; ACE-III, Addenbrooke's examination III; TE, Echo time; TR, Repetition time; FA, Flip angle; TI, Inversion time; FOV, Field of view; BMI, Body mass index; CSF, Cerebrospinal fluid.

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https://doi.org/10.1016/j.brainres.2024.149288
Received 3 May 2024; Received in revised form 28 June 2024; Accepted 18 October 2024
Available online 20 October 2024

features (Bachmann et al., 2024; Dadar et al., 2022). Chronic hyperglycemia may lead to vascular dysfunction and is suggested to be associated with diabetic peripheral neuropathy (DPN) (Dyck, 2011; Tesfaye, 2012). Here, knowledge of the localization and severity of WMHs could contribute to a deeper understanding of the natural history. T2-weighted magnetic resonance imaging (MRI) with fluid attenuated inversion recovery (FLAIR) images are utilized to identify WMHs. WMHs appear around the cerebral ventricles and/or in the deep subcortical white matter. WMHs are largely divided into periventricular WMHs suggested to be related to brain atrophy, neurodegeneration, and brain aging (Barber et al., 2000), and deep WMHs, suggested to be related to cerebrovascular events/chronic ischemia (Barber et al., 2000; Katsumata et al., 2010). The severity of WMHs can be assessed by classical semi-quantitative rating scales using visual evaluations by an observer (e.g. Fazekas scores (Fazekas, 1988)) or by using automated segmentation methods to assess volumetric measurements of the WMHs.

Hypertension is widely accepted as a risk factor of WMHs (Tamura and Araki, 2015). WMHs have also been associated with factors such as cognitive decline (Debette and Markus, 2010), functional disability (Tamura and Araki, 2015), gray matter atrophy (Wang et al., 2020), aging (Nyquist et al., 2015), and hyperglycemia (Nunley et al., 2015) depending on the location and severity of WMHs. The literature shows conflicting results regarding the presence, localization, and burden of WMHs in type 1 diabetes. Studies have shown greater WMH volumes in diabetes compared with controls (Grosu et al., 2021; Jacobson et al., 2022) and a study by Nunley et al. demonstrated that adults with type 1 diabetes had more severe WMH scores compared to non-diabetic participants (Nunley et al., 2015). The latter study found an association between higher WMH burden and cognitive decline and diabetic neuropathies whereas no association was found to blood pressure or hyperglycemia (Nunley et al., 2015). Other studies did not find increased WMHs in type 1 diabetes as compared to healthy controls (Thorn et al., 2019; Weinger et al., 2008). White matter disturbances based on DTI analysis have previously been associated with abnormal metabolite levels such as white matter N-acetylaspartate/creatine (NAA/cre) (Muthulingam et al., 2022) and HbA1c has shown a positive correlation with both periventricular and deep WMHs (De Bresser et al., 2010). It should be noted that most of the older studies are based on visual WMH rating scales, while newer automated quantitative analyses could be more sensitive in detecting differences in WMH burden including WMH volume and relative volume of WMHs.

To explore this topic, we based this study on a well-characterized cohort of adults with type 1 diabetes including three different neuropathic phenotypes of type 1 diabetes (with DPN and neuropathic pain, with DPN and without DPN) compared with matched healthy controls. In this diabetes cohort, we have previously shown reduced gray matter volume and altered functional connectivity, altered metabolite levels in both gray and white matter, and cognitive decline (Croosu et al., 2023a, 2023b, 2022; Hansen et al., 2024). In this present study, we explored WMHs (localization and burden) in different neuropathic phenotypes of type 1 diabetes including the relation to neuropathy measures and clinical characteristics.

Accordingly, the aims of this study were to 1) quantify periventricular and deep WMHs using A) conventional visual scoring assessed by Fazekas scale and B) automatic segmentation analysis and reporting of WMHs, 2) compare WMH measurements between adults with diabetes and healthy controls and between subgroups of diabetes, and 3) correlate WMH measurements to explanatory parameters and other risk factors in diabetes.

2. Results

The analyses included data from 56 adults with type 1 diabetes (50 % men, mean age 51.5 ± 9.1 years) and 20 healthy controls (50 % men, mean age 51.5 ± 9.2 years). The remaining 4 participants were excluded as two participants were not MRI scanned due to claustrophobia and two participants did not match the predefined subgroup criteria regarding the presence or absence of DPN using nerve conduction study.

Table 1 presents demographical and clinical data partially published previously elsewhere (Croosu et al., 2023a, 2023b, 2022) and results from the quantification of WMHs. No differences between type 1 diabetes and healthy controls were found in age ($p = 0.99$), sex ($p = 1.00$), body mass index (BMI) ($p = 0.07$), or systolic blood pressure ($p = 0.85$). The diabetes group had higher HbA1c than the controls as expected ($p < 0.001$) and the controls had higher diastolic blood pressure than the diabetes group ($p = 0.01$).

Using the Fazekas score, periventricular WMHs (mostly grade 1 and grade 3) were found in 66.1 % of participants with type 1 diabetes and 40.0 % of controls ($p = 0.063$), and deep WMHs (mostly grade 1) were found in 51.8 % of participants with type 1 diabetes and 50.0 % of controls ($p = 1.0$).

Using automated detection of WMHs, there were no significant differences in the count of periventricular WMHs ($p = 0.30$) or deep WMHs ($p = 0.31$) between participants with type 1 diabetes and controls. A higher periventricular lesion burden was present for the diabetes group as compared with controls ($p = 0.048$, see Fig. 1A), and the diabetes group showed a trend of higher absolute WMH volume and normalized WMH volume though not significant ($p = 0.059$ and $p = 0.066$, respectively). No significant differences were found for deep WMHs, but a trend towards higher normalized WMH volume was seen for the diabetes groups as compared with controls ($p = 0.052$).

Exploring the periventricular WMH lesion burden further in each subgroup (type 1 diabetes with painful DPN, type 1 diabetes painless DPN, type 1 diabetes without DPN, and healthy controls), there was a borderline but non-significant difference between type 1 diabetes with painless DPN and healthy controls ($p = 0.065$), a borderline difference between type 1 diabetes with painful DPN and healthy controls ($p = 0.065$) and no differences for the other subgroups comparisons (all $p > 0.1$), see Table 1 and Fig. 1B.

Exploring participants with DPN (painful and painless DPN) compared with participants without DPN (no DPN and healthy controls), the DPN group showed increased periventricular WMH lesion burden ($p = 0.024$), normalized WMH volume ($p = 0.026$), absolute volume ($p = 0.026$) but no significant differences in the count of WMHs ($p = 0.49$) or any of the deep WMH measurements (all $p > 0.19$).

In the diabetes cohort, periventricular WMH lesion burden was associated with age ($r = 0.59$, $p < 0001$), cognitive ACE-III language score ($r = -0.34$, $p = 0.006$), parietal white matter NAA/cre ratio ($r = -0.25$, $p = 0.034$), diastolic blood pressure ($r = -0.42$, $p < 0.001$), sural nerve amplitude ($r = -0.26$, $p = 0.026$), sural nerve conduction velocity ($r = -0.24$, $p = 0.036$), peroneal nerve amplitude ($r = -0.25$, $p = 0.034$), and peroneal nerve conduction velocity ($r = -0.23$, $p = 0.044$), relative gray matter volume ($r = -0.44$, $p < 0.001$), relative white matter volume ($r = -0.23$, $p = 0.045$), and relative CSF volume ($r = 0.40$, $p = 0.001$). No significant correlations of periventricular WMH lesion burden were found with HbA1c ($r = 0.21$, $p = 0.065$) or diabetes duration ($r = 0.22$, $p = 0.053$).

3. Discussion

In this study, we quantified periventricular and deep WMHs, using both visual Fazekas score and automatic detection, in adults with type 1 diabetes including participants with DPN (with and without pain) and without DPN as compared to healthy controls. Overall, the Fazekas scores and count of WMH lesions did not differ between the diabetes groups and controls, whereas the lesion burden assessed by automated detection was increased for adults with type 1 diabetes but only for periventricular lesions and not for deep WMHs. This was more pronounced for participants with DPN compared to no DPN. The periventricular lesion burden was further associated with more severe DPN characterized as poorer nerve conduction measurements, increased age, reduced cognitive function (language), and reduced volumetric and

Table 1
Cohort descriptions of demographics and clinical data for healthy controls and all participants with type 1 diabetes. Data for the subgroups of type 1 diabetes with neuropathy and neuropathic pain (DPN + pain), type 1 diabetes with neuropathy, and type 1 diabetes without neuropathy are further described.

	Healthy controls (n = 20)	All type 1 diabetes (n = 56)	p-value	All type 1 diabetes		
				DPN + pain (n = 19)	DPN (n = 19)	No DPN (n = 18)
Age (years)	51.5 ± 9.2	51.5 ± 9.1	0.99	51.4 ± 9.7	52.6 ± 9.0	50.6 ± 9.1
Sex (men/female)	10/10	28/28	1.00	9/10	10/9	9/9
BMI (kg/m^2)	24.3 (19.0–35.7)	27.2 (19.9–44.0)	0.07	27.3 (21.6–44.0)	27.8 (21.7–40.0)	27.0 (21.1–37.0)
HbA_1C (mmol/mol)	34 ± 3	69 ± 11	**<0.001***	70 ± 11	73 ± 10	63 ± 9
Diabetes duration (years)		29.1 ± 12.0		30.1 ± 14.0	33.7 ± 8.1	23.1 ± 11.0
Age of diabetes onset (years)		22.5 ± 14.5		21.3 ± 14.2	18.9 ± 10.9	27.5 ± 17.3
Retinopathy (n, %))	0 (0)	46 (82)	**<0.001***	18 (95)	17 (89)	11 (61)
Systolic BP (mmHg)	142.4 ± 21.5	143.3 ± 16.9	0.85	147.2 ± 22.4	143.7 ± 14.4	138.7 ± 11.6
Diastolic BP (mmHg)	89.7 ± 9.9	83.1 ± 10.2	**0.01***	84.6 ± 11.1	80.2 ± 9.9	84.5 ± 9.3
Suralis amplitude (uV)	10.3 (1.8–21.4)	2.3 (0.0–19.9)	**<0.001***	0.8 (0.0–19.9)	0.0 (0.0–5.6)	5.7 (1.3–16.1)
Suralis conduction velocity (m/sec)	54.5 (40.0–62.0)	38.5 (0.0–59.0)	**<0.001***	27 (0.0–59.0)	0.0 (0.0–50.0)	47.5 (41.0–54.0)
Peroneus amplitude (mV)	8.5 (2.7–35.8)	0.0 (0.0–31.8)	**<0.001***	0.0 (0.0–23.1)	0.0 (0.0–7.2)	6.3 (0–31.8)
Peroneus conduction velocity (m/sec)	53.0 (45.0–68.0)	0.0 (0.0–63.0)	**<0.001***	0.0 (0.0–61.0)	0.0 (0.0–52.0)	49.0 (0.0–63.0)
White matter NAA/cre	1.55 ± 0.13	1.41 ± 0.12[#]	**<0.001***	1.40 ± 0.14	1.37 ± 0.10[#]	1.46 ± 0.10
Relative gray matter volume (%)	43.3 ± 2.5	41.7 ± 2.9	**0.032***	41.5 ± 3.4	41.9 ± 3.2	41.6 ± 2.1
Relative white matter volume (%)	35.4 ± 2.2	34.2 ± 2.5	0.053	33.8 ± 3.1	34.5 ± 4.7	34.3 ± 2.1
Relative CSF volume (%)	21.4 ± 4.0	24.1 ± 4.6	**0.018***	24.7 ± 5.8	23.6 ± 4.4	24.1 ± 3.3
Total score ACE-III	94.0 (80.0–98.0)	90.0 (69.0–98.0)[#]	**0.032***	87.0 (72.0–97.0)	85.5 (73.0–97.0)[#]	92.5 (69.0–98.0)
Language score ACE-III	25.0 (23.0–26.0)	25.0 (20.0–26.0) [#]	**0.031***	24.0 (23.0–26.0)	24.5 (21.0–26.0) [#]	25.0 (20.0–26.0)
Memory score ACE-III	21.0 ± 3.1	18.6 ± 4.8 [#]	**0.016***	18.5 ± 5.2	17.5 ± 4.3[#]	20.4 ± 4.1
Fazekas scores						
Periventricular WMHs (n, %)						
No lesion	12 (60.0)	19 (33.9)	0.063	6 (31.6)	5 (26.3)	8 (44.4)
Any lesion	8 (40.0)	37 (66.1)		13 (68.4)	14 (73.7)	10 (55.6)
Grade 1	*4 (20.0)*	*18 (32.1)*		*7 (36.8)*	*5 (26.3)*	*6 (33.3)*
Grade 2	*0 (0.0)*	*1 (1.8)*		*1 (5.3)*	*0 (0.0)*	*0 (0.0)*
Grade 3	*4 (20.0)*	*18 (32.1)*		*5 (26.3)*	*9 (47.4)*	*4 (22.2)*
Deep white WMHs (n, %)						
No lesion	10 (50.0)	27 (48.2)	1.00	7 (36.8)	6 (31.6)	14 (77.7)
Any lesion	10 (50.0)	29 (51.8)		12 (63.2)	13 (68.4)	4 (22.2)
Grade 1	*8 (40.0)*	*25 (44.6)*		*10 (52.6)*	*11 (57.9)*	*4 (22.2)*
Grade 2	*2 (10.0)*	*3 (5.4)*		*1 (5.3)*	*2 (10.5)*	*0 (0.0)*
Grade 3	*0 (0.0)*	*1 (1.8)*		*1 (5.3)*	*0 (0.0)*	*0 (0.0)*
Automatic detection						
Periventricular WMHs						
Count (n)	6.5 (315)	7.0 (1–19)	0.302	7.0 (3–11)	9.0 (1–19)	7.0 (3–17)
Volume (cm^3)	0.32 (0.02–7.98)	1.09 (0.02–60.10)	0.059	1.19 (0.04–60.10)	1.38 (0.02–9.24)	0.73 (0.03–5.88)
Normalized volume (%)	0.02 (0.002–0.48)	0.07 (0.00–3.51)	0.066	0.09 (0.00–3.51)	0.10 (0.00–0.66)	0.05 (0.01–0.35)
Lesion burden (%)	0.06 (0.005–1.44)	0.21 (0.00–11.62)	**0.048***	0.29 (0.01–11.62)	0.30 (0.00–1.90)	0.13 (0.01–1.10)
Deep WMHs						
Count (n)	1.5 (0–16)	2.0 (0–16)	0.310	2.0 (0–10)	2.0 (0–16)	3.0 (0–6)
Volume (cm^3)	0.02 (0.00–0.24)	0.02 (0.00–0.43)	0.602	0.02 (0.00–0.43)	0.05 (0.00–0.30)	0.01 (0.00–0.20)
Normalized volume (%)	0.001 (0.00–0.026)	0.00 (0.00–0.030)	0.052	0.00 (0.00–0.03)	0.00 (0.00–0.02)	0.00 (0.00–0.01)
Lesion burden (%)	0.004 (0.00–0.053)	0.00 (0.00–0.09)	0.628	0.00 (0.00–0.90)	0.01 (0.00–0.06)	0.00 (0.00–0.04)

Fazekas scores and measurements from the automatic detection of WMHs are presented.
Note: Data are presented as mean±standard deviation, as numbers (n) or median (range). #one missing data. * $p<0.05$. Relative gray matter volume, white matter volume, and CSF volume refer to the absolute volumes normalized to intracranial volume in percentage. Normalized volume in percentage refers to absolute WMH volume normalized to intracranial volume in percentage and lesion burden is defined as absolute WMH volume normalized to total white matter volume in percentage.
Abbreviations: DPN: diabetic peripheral neuropathy, BMI: Body mass index, HbA1c: Hemoglobin A1c, BP: blood pressure, NAA: N-acetylaspartate, cre: creatine, CSF: cerebrospinal fluid, ACE-III: Addenbrooke's Cognitive Examination III.

metabolic brain measures. This points at changes associated with accelerated brain aging and neurodegeneration (which have been suggested to be reflected by periventricular WMHs) could be a key factor in the diabetic brain and supports the theories about central neuropathy.

When quantifying WMHs by traditional Fazekas score and count by the automated analysis, our findings showed that periventricular and deep WMHs in this cohort of adults with type 1 diabetes were not significantly different from healthy controls. A few studies reported no differences in WMH severity (Thorn et al., 2019; Weinger et al., 2008), whereas the study by Nunley et al. did find more severe WMHs (Nunley et al., 2015) between type 1 diabetes and controls. The studies used the Fazekas score, but the studies by Thorn et al. and Weinger et al. investigated younger participants and the study by Nunley et al. investigated participants with longer disease duration.

Our study did not demonstrate differences in deep WMH volume measurements between the diabetes group and healthy controls which could indicate that our diabetes cohort is not suffering from more chronic ischemic lesions than the age and sex-matched controls.

In general, periventricular WMHs with Fazekas grades 1 and 2 have been suggested to be of non-ischemic origin reflecting ependyma, gliosis, loosening of white matter fibers, and enlarging of the perivascular space, whereas deep WMHs are associated with ischemic tissue damage and marked arteriosclerosis with demyelination, gliosis, axonal degeneration, microglia activation with cytoplasmic vacuolation and increased tissue loss (Fazekas, 1988; Gouw et al., 2011). Fazekas grade 3 indicates the presence of extensive and severe white matter changes. Our study showed an even distribution between grade 1 and grade 3 for periventricular lesions in both groups, and grade 1 was most represented for deep lesions in both groups, indicating that changes in white matter observed in the present study could be more related to accelerated aging

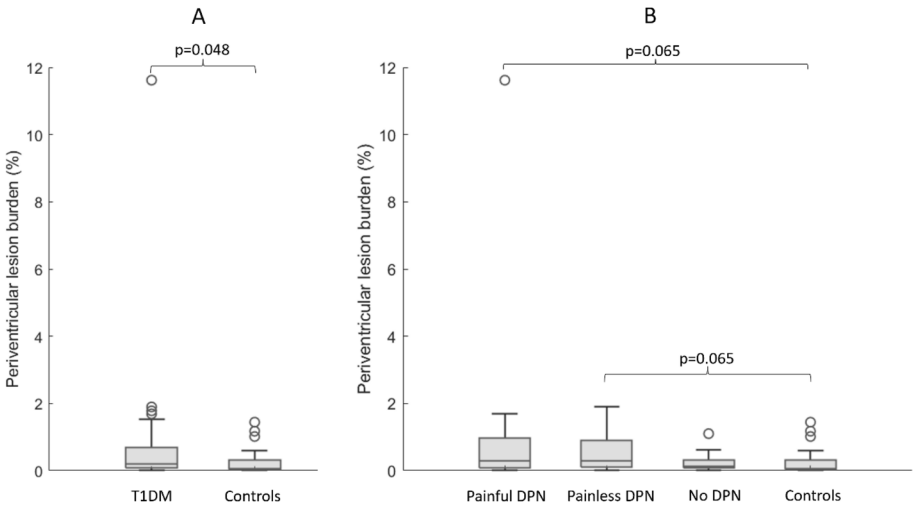

Fig. 1. Periventricular lesion burden (WMH volume normalized to total white matter volume) for the diabetes group (T1DM) and healthy controls (A) and all diabetes subgroups (painful diabetic peripheral neuropathy (DPN), painless DPN, no DPN) and healthy volunteers (B). P-values are provided for some comparisons. For other subgroups comparisons $p > 0.1$.

rather than severe white matter changes seen in some neurodegenerative diseases, e.g. groups with cognitive impairment and dementia (Dadar et al., 2022). As the study by Nunley et al. showed that type 1 diabetes had more severe WMHs (increased Fazekas score 2 and 3) compared with non-diabetic controls (Nunley et al., 2015), the characteristics of the group of type 1 diabetes and the control group could by important to consider.

When assessing WMH volume by the automated volumetric approach, the burden of periventricular lesions was significantly higher for the diabetes group in our present study. The studies by Jacobson et al. and Grosu et al. also showed higher WMH volumes in type 1 diabetes (Grosu et al., 2021; Jacobson et al., 2022). Our study investigated WMHs divided into periventricular and deep WMHs and our results indicated that it may not be sufficient to count the number of lesions, or use the Fazekas score, as it seems that the quantitative volumetric assessments, including the lesion burden as measured by the absolute WMH volume relative to total white matter volume, are more sensitive to detect differences between the investigated groups. One explanation could be that, if several small WMHs are close in location, these could increase in volume over time whereas the count will decrease as lesions merge even though the volume increases. Also, when the lateral ventricles expand into areas of tissue loss (shown as WMHs) (Jochems et al., 2022), this could also affect the number of detected WMHs. In the same diabetes cohort, we have previously found decreased gray matter volume and larger CSF volume, whereas white matter volume was lower but not significantly decreased (Croosu et al., 2022). Changes in tissue volumes have also been shown in other studies in type 1 and type 2 diabetes (Hansen et al., 2022; Jongen et al., 2007). Decreased gray matter volume reflects cortical atrophy, whereas a larger CSF volume may indicate subcortical atrophy. Both periventricular and deep WMHs are commonly associated with enlarged ventricles (Jochems et al., 2022). As expected, the periventricular WMH lesion burden in our study was correlated positively with CSF volume and negatively with gray and white matter volume.

Our results demonstrated increased periventricular lesion burden in the overall diabetes group as compared to healthy controls, which was more pronounced in type 1 diabetes with DPN as compared to type 1 diabetes without DPN. Also, the periventricular lesion burden was correlated with nerve conduction measurements both for the sensory and motor nerves, supporting knowledge of co-existence and interplay between peripheral and central nervous system alterations in diabetic neuropathy. Only a few studies explored the role of peripheral neuropathy and WMHs, whereas many of the studies excluded participants with neuropathies. The study by Nunley et al. showed that diabetes-related neuropathies were a significant predictor of high WMH volume (Nunley et al., 2015). In the present study, we showed an association between increased periventricular lesion burden and decreased parietal white matter NAA/cre, where decreased NAA is considered as a marker for neuronal loss or dysfunction. This is in line with a previous study showing that white matter integrity was disrupted in adults with type 1 diabetes and associated with peripheral neuropathy and lower parietal NAA/cre metabolite ratio (Muthulingam et al., 2022). The associations between the presence of DPN, reduction in nerve conduction function and increase in lesion burden of periventricular WMHs could reflect underlying non-ischemic microvascular disease mechanisms including aspects of increased neurodegeneration and accelerated brain aging. As the periventricular WMH lesion burden in the diabetes cohort was also associated with a decrease in relative gray and white matter volume, white matter NAA/cre reduction, increased age, and a decrease in cognitive language function, this could suggest that diabetic neuropathy at both the central and peripheral level might be linked to neurodegenerative processes and accelerated brain aging. All these results could reflect accelerated neurodegeneration as also suggested by Habes et al. demonstrating that participants with type 1 diabetes had higher brain age as compared to healthy controls (Habes et al., 2023). Demyelination and damage to axons are observed in aging and neurodegenerative diseases (Chen et al., 2020) and in this study the WMH burden could reflect the cumulative effects of different cellular and molecular mechanisms.

Overall, the inconsistency in the literature about WMH severity in type 1 diabetes and DPN might be explained by differences in demographic and disease characteristics (e.g. age, disease duration of the cohorts, overweight, complications to diabetes or metabolic syndromes), phenotypes of the cohorts, partly age-related confounders, etc. In this study, we investigated subgroups of different neuropathic phenotypes which were age and sex-matched between subgroups. This has advantages in the comparison between groups, but it may also not reflect the clinical majority of the clinical characteristics as, for instance, the group without DPN had relatively long diabetes duration compared to the representative clinical population, and the subgroups were not large or matched on diabetes duration. A limitation of this study was the small sample size of the subgroups. Some of the results showed marginal differences and this could lead to inability to detect a substantial difference as statistically significant. Furthermore, longitudinal studies are needed to provide further insights into the development and progression of brain changes related to type 1 diabetes and DPN, and how white

matter changes can be used to understand the potential link between diabetes, central and peripheral neuropathy, and how this may reflect neurodegeneration and accelerated brain aging. Finally, the traditional Fazekas scores and WMH measurements from automatic detection methods are based on different definitions as described in the methods section. The novelty and clinical significance of detecting and quantifying WMHs as a marker of white matter changes relates to the potential of supporting early diagnosis, risk stratification and personalized treatment approaches. This knowledge can enhance understanding and management of neurodegenerative conditions associated with white matter changes.

The use of different neuroimaging techniques has enabled multimodal information which is important in the understanding of the underlying mechanisms of changes in the central nervous system in diabetes and DPN. In the same cohort, we have previously investigated volumetric brain structure (Croosu et al., 2022), resting state function (Croosu et al., 2023b), brain metabolites (Hansen et al., 2024), and cognitive function (Croosu et al., 2023a). Thus, investigations with different MRI techniques that provide supplementary information may add additional knowledge to the underlying brain mechanisms in diabetes. For instance, DTI with the assessment of white matter fiber tracts could be used for detecting "invisible" microstructural alteration of white matter integrity, which may add information to this knowledge. Also, more detailed analyses of WMH lesions could hold more information regarding the shape and texture (Yuan et al., 2021).

The purpose of this study was to explore WMHs in different neuropathic phenotypes of type 1 diabetes in order to get more knowledge about the localization and burden of white matter lesions as compared with healthy controls and to investigate associations to clinical characteristics. The differences in WMHs were only detected using the automatic detection of the lesion burden whereas the traditional Fazekas score did not show differences between groups. As the volumetric burden of WMHs was larger only for the periventricular location and associated with both DPN and other MRI features of the brain, this indicates, that peripheral and central neuropathic changes co-exist in type 1 diabetes. However, with the limitations of this study, larger studies and longitudinal studies are needed to provide more insight into the development and progression of brain changes related to type 1 diabetes and DPN. Our findings indicate that diabetic neuropathy in type 1 diabetes could be related to brain alternations reflecting neurodegenerative processes and accelerated aging.

4. Experimental Procedure

4.1. Study participants and characteristics

Sixty adults with type 1 diabetes and 20 matched healthy controls participated in the MEDON study (Methods of Early Detection of diabetic peripheral Neuropathy) in the period between August 2019 and April 2021. Participants were recruited through the outpatient clinics at Department of Endocrinology and Steno Diabetes Center North Denmark, Aalborg University Hospital, Denmark, and a local database (healthy controls). MRI scans were performed at Department of Radiology, Aalborg University Hospital, Denmark. The North Denmark Region Committee on Health Research Ethics (N-20190003) approved the study and informed written consent was obtained from all participants. The study was conducted according to the Declaration of Helsinki. Study details were registered at clinicaltrials.gov (NCT04078516). Age between 18–70 years was an inclusion criterion. MRI contraindications were considered as an exclusion criterion as well as abnormalities in the thyroid- or parathyroid metabolism, impaired liver- or kidney function, history or current alcohol abuse and/or drug abuse, cancer or history of chemotherapy, presence of chronic viral infections, severe skin disease, critical ischemia of the lower extremities, and pregnancy. Participants were age (+/- 2 years) and sex-matched across the four subgroups consisting of 20 participants in each subgroup including 1) type 1 diabetes and painful DPN, 2) type 1 diabetes screened for probable painless DPN (according to the Toronto Consensus (Tesfaye et al., 2010)) based on peripheral vibration perception threshold above 25 V, 3) type 1 diabetes without DPN and 4) healthy controls. Clinical and experimental data such as diabetes duration, HbA1c, retinopathy status, blood pressure, and nerve amplitude and conduction velocity of the sural and peroneal nerves of the right leg were assessed for all participants. Further description of the study methods and results can be found in (Croosu et al., 2023a, 2023b, 2022; Røikjer et al., 2023d, 2023a, 2023b, 2023c, 2022, Hansen et al. 2024). Additional experimental measurements, which were already shown to be altered in this cohort were explored in relation to WMH measurements. Analysis of cognitive function assessed by Addenbrooke's examination III (ACE-III) questionnaire showed that type 1 diabetes participants had lower total ACE III, memory, and language scores (Croosu et al., 2023a), analysis of brain metabolites assessed by MR spectroscopy showed lower NAA/cre in participants with type 1 diabetes and DPN (Hansen et al., 2024) and analysis of brain volumes assessed as relative gray matter volume, white matter volume, and cerebrospinal fluid (CSF) volume (absolute volumes normalized to intercranial volume in percentage) (Croosu et al., 2022) were altered.

4.2. MRI data acquisition and WMH analyses

The MRI scans were obtained from a 3 T scanner (GE Signa Premier, General Electric, Milwaukee, WI, USA) with a 48-channel head coil. Structural T1-weighted images (MPRAGE) were acquired with an echo time (TE) of 3.6 ms, repetition time (TR) of 8.4 ms, a flip angle (FA) of 8°, inversion time (TI) of 900 ms, a recovery time of 700 ms, a slice thickness of 0.8 cm, and a field of view (FOV) of 25 cm. FLAIR images were acquired with the following parameters: 32 slices, FA of 160°, TE of 120 ms, TR of 9000 ms, TI of 2465 ms, slice thickness of 5 cm, and FOV of 24 cm.

MRI scans were evaluated by a neuroradiologist blinded to the clinical data for all participants. Using Fazekas score, deep WMHs were graded into absent (grade 0), punctate (grade 1), early confluent (grade 2), and confluent (grade 3) abnormalities, and periventricular WMHs (lesions located within 13 mm from the lateral ventricles) into absent (grade 0), 'cap' or pencil-thin lining (grade 1), smooth 'halo' (grade 2), irregular periventricular lesions extending into the deep white matter (grade 3) (Fazekas, 1988).

An automated MRI brain volumetry program was utilized (volBrain.net) to obtain quantitative information on WMHs (Coupé et al., 2018; Manjón and Coupé, 2016). Only lesions located as periventricular and deep white matter lesions were considered further in this study (lesions located juxtacortical and infratentorial were not included). T1-weighted images and FLAIR images were analyzed through the lesionBrain-pipeline (Coupé et al., 2018). Lesions located periventricular (lesions located within 3 mm from the lateral ventricles) and in deep white matter (lesions located minimum 3 mm away from the lateral ventricles, the gray matter (e.g. cortex), and the union of brainstem and cerebellum) were reported from the automatic analysis quantified as count, absolute WMH volume in cm^3, normalized volume in percentage (absolute WMH volume normalized to intracranial volume) and as lesion burden in percentage (absolute WMH volume normalized to total white matter volume) (Coupé et al., 2018; Manjón and Coupé, 2016). Fig. 2 illustrates examples of MRI scans and the corresponding WMH segmentation results for subjects with different severity and localizations of white matter lesions.

4.3. Statistical analyses

Differences in demographics and clinical data between the diabetes group and healthy controls were investigated using an independent sample *t*-test, Mann-Whitney *U* test, or chi-squared test as appropriate. Fisher's exact test was used to test differences in the absence/presence

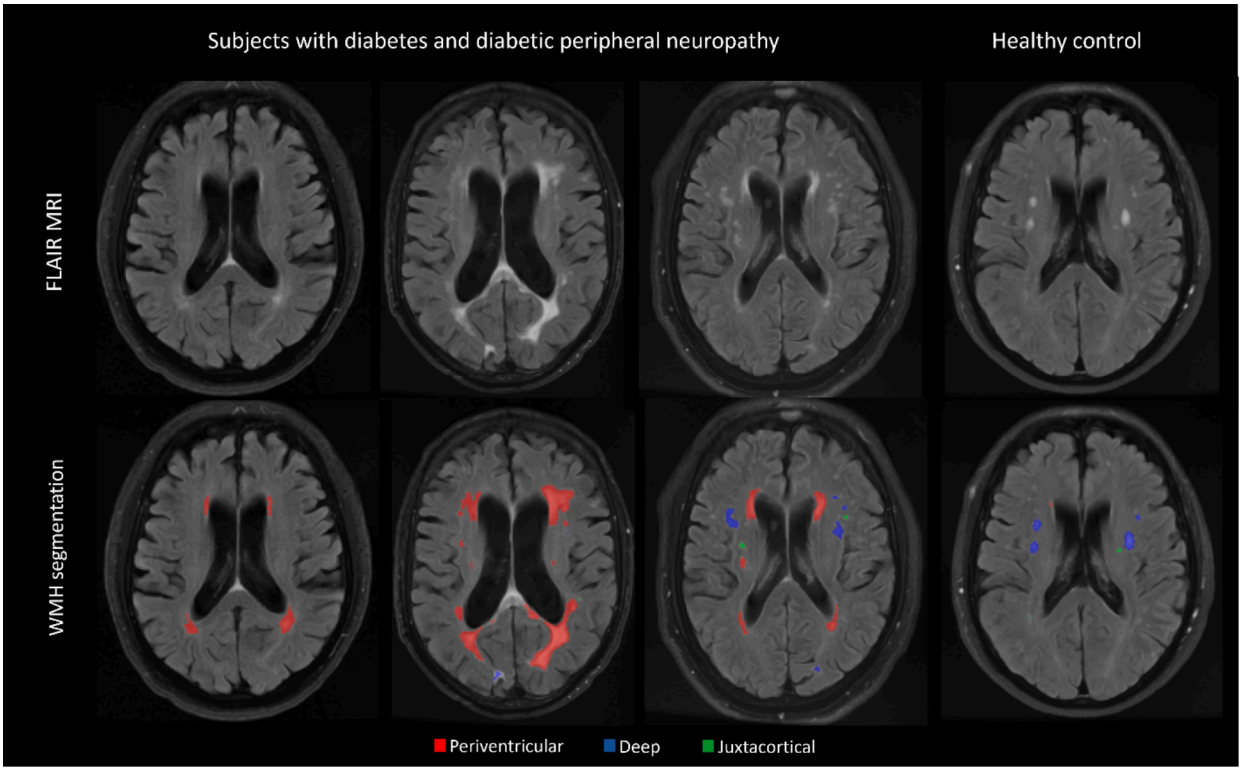

Fig. 2. Brain MRI (FLAIR) (in upper panel) and corresponding automatic lesionBrain WMH segmentation results (lower panel) in four representative subjects with different severity and localization of the WMHs. The first 3 scans are subjects with diabetes and DPN, and the last subject is a healthy control subject. Colors show the automatic detection of lesions illustrated in red (periventricular, within 3 mm from the ventricles), green (juxtacortical, with 3 mm from the cortex), and blue (deep, more than 3 mm from the ventricles and cortex).

(any grade) of Fazekas periventricular and deep WMH scores between groups. To compare WMH measurements from the automatic detection method between the diabetes group and healthy controls, between diabetes subgroups, and between participants with DPN (painful and painless DPN) and without DPN (no DPN and healthy controls), Mann Whitney U tests were performed due to non-normal distribution of the data. Correlations of the significant WMH measures to explanatory parameters and other risk factors were explored using Spearmans correlation analyses including only participants with diabetes. We explored the hypothesis that increased WMHs were associated with higher age, longer diabetes duration, poorer glycemic control, cognitive decline, decreased NAA/cre levels in white matter, gray and white matter atrophy, and poorer nerve conduction measurements using a one-sided test. Data are presented as mean ± standard deviation unless otherwise stated. $P < 0.05$ was considered significant. As this study included explorative analyses, corrections for multiple comparisons were not applied. The statistical analyses were performed in IBM SPSS Statistics (IBM Corp. Released 2021. IBM SPSS Statistics for Windows, Version 29.0. Armonk, NY: IBM Corp.).

CRediT authorship contribution statement

Tine M. Hansen: Conceptualization, Data curation, Formal analysis, Methodology, Writing – original draft. **Suganthiya S. Croosu:** Writing – review & editing, Project administration, Methodology, Investigation, Data curation, Conceptualization. **Shahram Kianimehr:** Writing – review & editing, Methodology, Formal analysis, Data curation. **Mimoza Gjela:** Writing – review & editing, Methodology, Formal analysis, Data curation. **Johan Røikjer:** Writing – review & editing, Project administration, Methodology, Investigation, Conceptualization. **Yousef Yavarian:** Writing – review & editing, Methodology, Conceptualization. **Carsten D. Mørch:** Writing – review & editing, Conceptualization. **Niels Ejskjaer:** Writing – review & editing, Supervision, Methodology, Investigation, Conceptualization. **Jens B. Frøkjær:** Writing – original draft, Supervision, Methodology, Funding acquisition, Formal analysis, Data curation, Conceptualization. Niels Ejskjaer was the guarantor and clinically responsible for the recruitment, clinical characterization, and investigations of all subjects included. Jens B. Frøkjær was responsible for the MRI investigations.

Funding

This work was partly supported by Augustinus Fonden, Denmark [grant no.19-1302] but the funding source did not influence the study.

Acknowledgments

Acknowledgments: Kenneth K. Jensen, Department of Radiology, Aalborg University Hospital, Denmark assisted in the collection of MRI data.

Data availability

Data will be made available on request.

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