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MRI evaluation of the relationship between carotid artery endothelial shear stress and brain white matter lesions in migraine

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Abstract

Although white matter lesions are frequently detected in migraine patients, underlying mechanisms remain unclear. Low carotid artery endothelial shear stress has been associated with white matter lesions. We aimed to investigate the association between carotid artery endothelial shear stress and white matter lesions in migraine. In 40 elderly migraine patients ($n = 29$ females, 75 years [SD 3]) and 219 controls ($n = 80$ females, 74 years [SD 3]) from the PROSPER-MRI study, carotid artery endothelial shear stress was estimated on 1.5 T gradient-echo phase contrast MRI. White matter lesion volumes were calculated from structural MRI scans. Analyses were adjusted for age, sex, cardiovascular risk factors and cardiovascular disease. Migraine patients had lower mean endothelial shear stress compared to controls (0.90 [SD 0.15] vs. 0.98 [SD 0.16] Pa; $P = 0.03$). The association between mean endothelial shear stress and white matter lesion volume was greater for the migraine group than control group (P for interaction $= 0.05$). Within the migraine group, white matter lesion volume increased with decreasing endothelial shear stress (β-0.421; $P = 0.01$). In conclusion, migraine patients had lower endothelial shear stress which was associated with higher white matter lesion volume.

Keywords

Cerebrovascular disease, endothelial shear stress, hemodynamics, magnetic resonance imaging, migraine

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Introduction

Migraine is a common, multifactorial, neurovascular disorder characterized by recurrent attacks of headache accompanied with autonomic nervous system dysfunctions and, in one-third of patients, aura symptoms.[1] The prevalence of brain white matter lesions (WMLs) is increased in migraine patients, which has not been explained by traditional cardiovascular risk factors or atherosclerosis.[2–5] Some studies suggested that endothelial or arterial dysfunction might predispose individuals to brain WMLs.[6,7]

Endothelial shear stress is an important regulator of endothelial function and is defined as the tangential force exerted on the endothelial cells by viscous blood flow. Sufficiently high endothelial shear stress is essential for endothelial homeostasis as it optimizes endothelial structure and function by inducing the release of agents with antithrombotic and anti-inflammatory properties.[8] In contrast, low or highly fluctuating endothelial shear stress has a deleterious effect on the endothelium by decreasing nitric oxide (NO) and increasing endothelin-1 levels.[9] Low endothelial shear stress also induces endothelial apoptosis, endothelial

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cell shape transformation and promotes sub-endothelial accumulation of low-density lipoprotein cholesterol.[10,11] Previously, low endothelial shear stress in the carotid arteries has been associated with cerebrovascular pathology such as brain WMLs.[12–17]

In the present study, we aimed to evaluate whether migraine is associated with reduced carotid artery endothelial shear stress. Moreover, we aimed to explore the association between carotid artery endothelial shear stress and WML volume in migraine.

Material and methods

Study design and participants

Data were obtained from the baseline measurements of the PROSPER MRI substudy, a large randomized controlled trial assessing the benefits of 40-mg pravastatin daily on vascular outcomes, of which the design has been described in detail elsewhere.[18,19] At baseline (before start of the study medication), 554 participants were enrolled in the MRI substudy of whom 329 underwent MRI of both the internal carotid arteries and cranium. Of these 329 participants, 40 had migraine, 219 had no history of headache (controls). The remaining 70 participants were excluded because of missing or incomplete ($n = 13$) headache questionnaire, presence of non-migraine headaches ($n = 11$) or migraine-like headache ($n = 46$). All participants refrained from smoking for at least 90 min before examination. The institutional review board of the Leiden University Medical Center approved the protocol for the MRI study. The study was conducted in accordance with the Declaration of Helsinki (1983). All participants gave written informed consent and agreed with future retrospective analyses.

Migraine status

Lifetime migraine status, defined as current or past migraine, was assessed by trained research nurses using validated headache questionnaires (sensitivity 95%; specificity 100%),[20] according to classification of the International Headache Society criteria of 2004.[21] All subjects also fulfilled the new criteria of 2013.[1] Two migraine experts evaluated all questionnaires and decided on the final diagnosis.

MRI measurements

Flow measurements in the internal carotid arteries were performed on a 1.5-Tesla MRI platform (Gyroscan ACS-NT 15; Philips Medical Systems) using a gradient echo phase-contrast technique (repetition time 14.7 ms; echo time 9.1 ms; flip angle 7.5°; slice thickness 5 mm; matrix 256×154; field of view 250×188 mm; and velocity encoding 100 cm/sec and one number of signal averages), in the plane perpendicular to the vessel, 40 mm from the carotid bifurcation. Retrospective cardiac triggering by means of a peripheral pulse unit was applied, resulting in 16 phases over a cardiac heart cycle. The images were analyzed using the software package FLOW® (Division of Image Processing, LKEB, Department of Radiology, Leiden University Medical Center).[22,23] With this semi-automatic method, the vessel has to be identified manually, after which the delineation of the vessel is established automatically.

Calculation of endothelial shear stress

Velocity profiles were approximated by a previously described three-dimensional paraboloid method.[24] Endothelial shear stress was calculated

$$Endothelial\ shear\ stress = \mu \cdot shear\ rate$$

$$Shear\ rate = Vmax \cdot \sqrt{(2\pi \cdot Vmax/Q)}$$

where μ represents the blood viscosity, Q the blood flow volume, and V_{max} the maximum velocity over the cross section of the vessel. Blood viscosity and its shear thinning properties were modeled using the Carreau-Yasuda model, individually adjusted for hematocrit

$$\mu = 2.2 + (22 - 2.2) \cdot (1 + (0.11 \cdot shear\ rate)^{0.644})^{(hematocrit-1)/0.644}$$

Endothelial shear stress during the 16 phases of one cardiac cycle was clustered into early (4–6), mid (7–9) and late diastolic (10–12) and peak systolic (15–0) endothelial shear stress.[16] The average endothelial shear stress during the cardiac cycle was defined as mean endothelial shear stress. Figure 1 shows an example of endothelial shear stress during the cardiac cycle and illustrates how the cardiac phases were subdivided. Measurements from both internal carotid arteries were averaged.

Brain WMLs

WMLs were assessed using in-house-developed semi-automated software which is described in detail elsewhere.[25] Briefly, WMLs were defined as regions being hyperintense on both proton density-weighted MRI and T2-weighed MRI. Infratentorial WMLs were excluded. The automatically generated WMLs maps

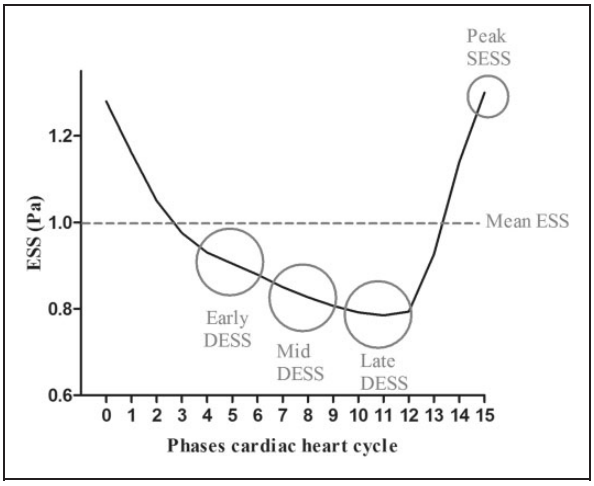

Figure 1. Endothelial shear stress during one cardiac cycle. DESS: diastolic endothelial shear stress; ESS: endothelial shear stress; SESS: systolic endothelial shear stress.

were edited and reviewed by a trained rater with 20 years of neuroradiological experience, blinded to subject identity and diagnosis. WMLs were divided into periventricular or deep WMLs, depending on their connection to the lateral ventricles.

Statistical analysis

Data are presented as mean ± SD or as number (percentage). Baseline characteristics were compared between the groups using a Students *t* test for continuous variables and a Chi square test for categorical variables. Distributions of continuous variables were examined for normality and logarithmically transformed when appropriate (total WMLs, deep WMLs, periventricular WMLs). Median (interquartile range) are reported for original values of variables that were logarithmically transformed.

Generalized linear models were used and corrected for age, sex, smoking, systolic blood pressure, diastolic blood pressure, serum cholesterol, history of hypertension, history of diabetes mellitus and history of vascular disease. Associations between mean internal carotid artery endothelial shear stress with WML volumes were additionally adjusted for total intracranial volume. Regression lines between mean endothelial shear stress and WML volumes were compared in subjects with and without migraine by adding an interaction term (presence of migraine × mean endothelial shear stress) to the models. Z-values were calculated for standardization of variables. The association of mean endothelial shear stress and WML volumes in migraine patients and controls are presented as standardized Betas with corresponding *P*-values. Analyses were performed before and after stratification by sex, based on earlier observations of increased risk of WMLs only among female migraine patients.[3] For all analyses, SPSS software was used (IBM SPSS Statistics for Windows, Version 23.0 Armonk, NY: IBM Corp.). Statistical significance was defined as a two tailed $P < 0.05$, and $P < 0.1$ for interaction terms.

Table 1. Baseline characteristics of study participants ($n = 259$).

	Migraine N = 40	Control N = 219	*P*-value
Age, y	74.8 ± 3.1	74.4 ± 3.2	.47
Female	29 (73)	80 (37)	<.001
Body mass index, kg/m^2	26.5 ± 4.0	26.5 ± 3.6	.96
Systolic blood pressure, mm Hg	157 ± 18	157 ± 22	.87
Diastolic blood pressure, mm Hg	87 ± 12	85 ± 11	.17
Total cholesterol, mmol/L	5.9 ± 0.9	5.7 ± 0.9	.41
Low-density lipoprotein, mmol/L	4.0 ± 0.8	3.9 ± 0.8	.58
High-density lipoprotein, mmol/L	1.3 ± 0.3	1.2 ± 0.3	.28
Current smoking	5 (13)	44 (20)	.26
History of hypertension	34 (85)	134 (61)	.004
History of diabetes mellitus	6 (15)	34 (16)	.93
History of vascular disease[a]	15 (38)	100 (46)	.34
Anti-hypertensive use			
Diuretics	17 (43)	59 (27)	0.047
ACE inhibitors	16 (40)	64 (29)	0.18
Beta blockers	8 (20)	75 (34)	0.08
Calcium channel blockers	7 (18)	52 (24)	0.39
Anti-thrombotics use			
Aspirin	14 (35)	69 (32)	0.66
Anti-coagulants	1 (3)	10 (5)	0.55
Migraine diagnosis			
With aura	16 (40)	N.A.	N.A.
Without aura	21 (53)	N.A.	N.A.
Doubt about aura status	3 (8)	N.A.	N.A.
Internal carotid arteries			
Flow (mL/min)	190.2 ± 39.7	195.7 ± 37.4	.40
Maximum velocity (cm/s)	24.7 ± 3.8	26.2 ± 4.5	.05
Blood viscosity (mPa·s)	5.2 ± 0.5	5.3 ± 0.5	.30

Values are n (%) or mean ± SD. [a]Any of stable angina, intermittent claudication, stroke, transient ischemic attack, myocardial infarction, peripheral arterial disease surgery or amputation for vascular disease more than six months before study entry.

Results

Table 1 shows the characteristics of the migraine and control group. In the migraine group, females were overrepresented (73% vs. 37%, $P < 0.001$), reflecting the normal sex predilection of migraine in women. Migraine patients more often had a history of hypertension (85% vs. 61%, $P = 0.004$), and consequently the use of diuretics was higher in the migraine group compared with controls (43% vs. 27%, $P = 0.047$). Use of

Table 2. Internal carotid artery endothelial shear stress in migraine patients and controls.

	Migraine	Control	*P*-value
All	$n = 40$	$n = 219$	
Mean ESS	0.90 ± 0.15	0.98 ± 0.16	**.03**
Early diastolic ESS	0.85 ± 0.14	0.92 ± 0.15	**.04**
Mid diastolic ESS	0.77 ± 0.12	0.83 ± 0.13	**.04**
Late diastolic ESS	0.73 ± 0.14	0.79 ± 0.12	**.04**
Peak systolic ESS	1.17 ± 0.19	1.31 ± 0.24	**.01**
Female	$n = 29$	$n = 80$	
Mean ESS	0.88 ± 0.15	0.97 ± 0.16	**.03**
Early diastolic ESS	0.83 ± 0.13	0.90 ± 0.15	**.04**
Mid diastolic ESS	0.75 ± 0.12	0.82 ± 0.13	**.02**
Late diastolic ESS	0.71 ± 0.15	0.77 ± 0.12	**.04**
Peak systolic ESS	1.14 ± 0.20	1.29 ± 0.25	**.02**
Male	$n = 11$	$n = 139$	
Mean ESS	0.96 ± 0.12	0.99 ± 0.15	.84
Early diastolic ESS	0.90 ± 0.13	0.93 ± 0.15	.84
Mid diastolic ESS	0.84 ± 0.13	0.84 ± 0.13	.87
Late diastolic ESS	0.79 ± 0.09	0.80 ± 0.12	.93
Peak systolic ESS	1.24 ± 0.17	1.32 ± 0.24	.62

ESS: endothelial shear stress. Note: Data are presented in Pascal (Pa) with means ± SD. *P*-values are adjusted for age, sex, smoking, systolic blood pressure, diastolic blood pressure, serum cholesterol, history of hypertension, history of diabetes mellitus and history of vascular disease. Bold values represent significant results ($P < 0.05$).

other antihypertensive and anti-thrombotic medication was similar between the groups.

Endothelial shear stress

After adjustment for age, sex and cardiovascular risk factors and disease, mean, diastolic and systolic endothelial shear stress was significantly lower in the migraine group as compared to the control group (all $P < 0.05$) (Table 2). Stratified analyses by sex showed significantly lower mean, diastolic and systolic endothelial shear stress in the female migraine patients compared to female control subjects. Although in males the same trend was shown, this did not reach statistical significance (Table 2).

WMLs

In migraine patients, median (interquartile range) total WML volume was 1.65 (0.7–5.6) mL, deep WML was 0.66 (0.1–1.2) mL, and periventricular WML was 1.22 (0.4–4.2) mL. In control subjects, median (interquartile range) total WML was 1.32 (0.4–5.3) mL, deep WML was 0.30 (0.09–1.3) mL, and periventricular WML was 0.95 (0.2–4.0) mL. The median WML volumes were thus higher in migraine patients compared to control subjects, although not statistically significant (all $P > 0.05$). Stratification by sex similarly revealed no differences in WML volume between migraine patients and controls (all $P > 0.05$).

We compared the slope of the regression lines between mean endothelial shear stress and WML volumes in migraine patients and controls (Figure 2). Figure 3 shows the associations between endothelial shear stress and WML volumes in migraine patients and controls as standardized beta coefficients with 95% confidence intervals. The observed significant interaction effects ($P < 0.1$) indicate that the influence of endothelial shear stress on total and deep WML volumes was greater for migraine group than the control group. Within the migraine group, decreasing endothelial shear stress was associated with increasing total WML volume ($\beta = -0.421$; $P = 0.01$), deep WML volume ($\beta = -0.407$; $P = 0.02$) and periventricular WML volume ($\beta = -0.378$; $P = 0.02$). In the control group, associations did not reach statistical significance. Stratified analyses showed that these effects were only visible among females (Figure 3).

Discussion

In this study, we demonstrate that migraine patients have lower carotid artery endothelial shear stress compared to controls. Furthermore, in migraine patients, a lower endothelial shear stress was associated with higher WML volume. This provides new insights in the well-known associations between migraine and brain WMLs.

Low endothelial shear stress is associated with endothelial dysfunction.[8,26] In line with the current finding of lower endothelial shear stress in migraine patients, some previous studies that assessed peripheral vascular reactivity in response to physiologic or pharmacologic stimuli in migraine patients suggested impaired endothelial-dependent vascular reactivity.[27] Moreover, biochemical alterations, indicating changes in endothelial activation, have also been reported,[28] and studies evaluating peripheral arterial function in migraine are pointing at increased stiffness or reduced compliance of the arterial system.[27] Recently, women suffering from migraine with aura showed higher levels of circulating endothelial microparticles, a surrogate for endothelial dysfunction.[29]

Present findings of decreased carotid artery endothelial shear stress in migraine invite to speculate on the nature of the relationship. We have to note that, as this was a cross-sectional study, we cannot determine the direction of the associations between migraine and the decreased carotid artery endothelial shear stress. Low endothelial shear stress has deleterious effects on the

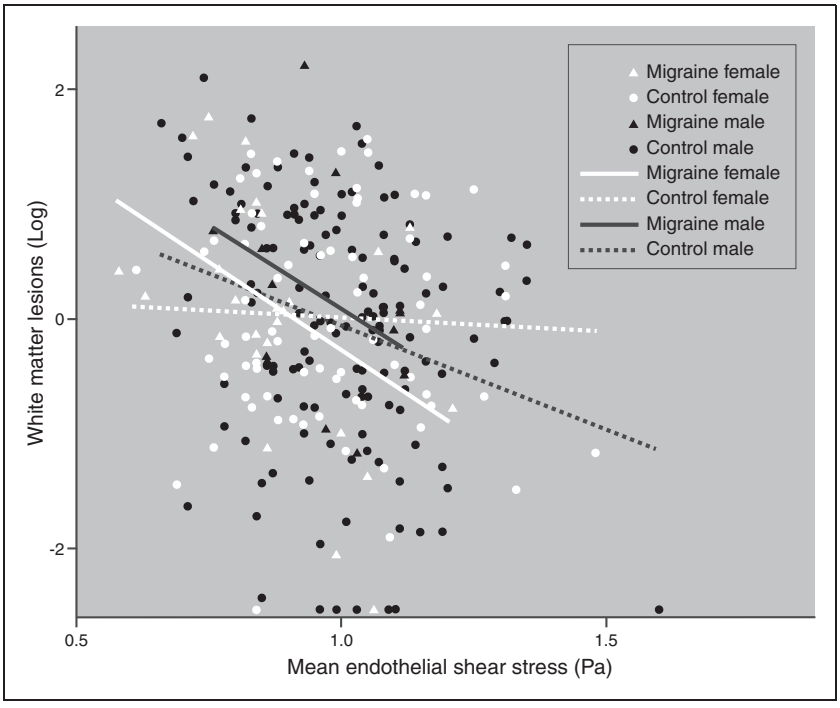

Figure 2. Scatterplot between mean endothelial shear stress and total white matter lesions showing regression lines for the migraine and control group, stratified by sex.

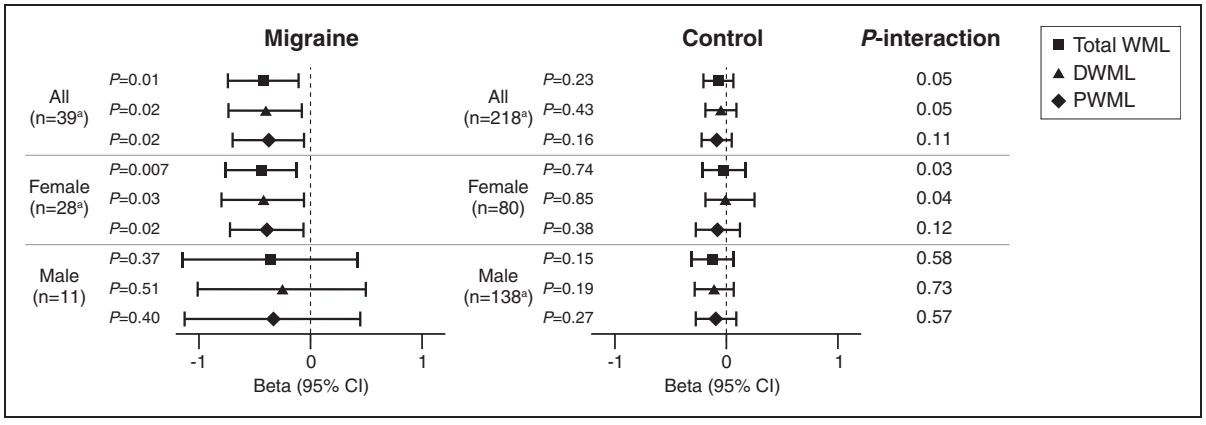

Figure 3. Associations between endothelial shear stress and white matter lesions.
WML: white matter lesions; DWML: deep white matter lesions; PWML: periventricular white matter lesion.
The associations as standardized beta with 95% confidence intervals (CI) between mean endothelial shear stress and white matter lesion volumes in all migraine patients and controls and stratified by sex.
[a]For these analyses, 1 female migraine patient and 1 male control were excluded, because of missing total intracranial volume measurements.

endothelium by decreasing NO and increasing endothelin-1 levels.[9] Possibly, shear stress induces endothelial changes on the capillary level that directly modifies neuronal and astrocytic function. This hypothesis has been derived from observations in rodents showing that NO deprivation lowered the threshold for a cortical spreading depression, the assumed pathophysiological correlate of the migraine aura.[30–32] This suggests connections between the neuronal and astrocytic network and the vascular tree and may provide an explanation for the found associations between reduced endothelial shear stress (and endothelial dysfunction) in migraine. Another possibility is that migraine-related risk factors predispose to decreased endothelial shear stress. Hypertension was indeed more prevalent in the current group of migraine patients. Nevertheless, the

adjustment of our findings for vascular risk factors and diseases (smoking, blood pressure, serum cholesterol, history of hypertension, history of diabetes mellitus and history of vascular disease) did not influence the results. Therefore, we find it less likely that these common cardiovascular risk factors have driven the found association. Lastly, migraine has been proposed as a systemic vascular disorder characterized by a (chronic, probably slight) pro-inflammatory, pro-coagulatory or otherwise vasculopathic state.[33] Such chronic conditions could predispose to a gradual development of vascular wall changes in migraine patients, which finally may lead to unfavorable hemodynamics, including lower endothelial shear stress. This may be only measurable at older age.

The finding of increased WML volume with decreasing endothelial shear stress has been described previously in the PROSPER study.[16] In the present study, we observed significant interaction effects indicating that the influence of endothelial shear stress on development of WML is greater for the migraine group compared to the control group. In the control group, we could no longer demonstrate a significant effect between endothelial shear stress and WMLs. It seems plausible that in the earlier PROSPER study the association was notably driven by migraine. Vasculopathic changes of the intracranial microvasculature, possibly leading to changed compliance,[34] are likely a direct cause of brain WMLs. Possibly, a combination of decreased endothelial shear stress (resulting in endothelial dysfunction) and local neurovascular changes during migraine attacks such as activation of the clotting system[35] and neurogenic inflammation,[36] affect the vulnerable small deep penetrating arteries in migraine patients and result in higher burden of WMLs in these patients.

A limitation of this study is the cross-sectional design. As a result, we cannot determine the direction of the association between migraine, carotid artery endothelial shear stress and brain WMLs. Therefore, future studies are warranted to determine whether the associations represent a causal relationship. Another limitation is the study population which consists of elderly migraine patients at increased risk for cardiovascular disease. This may hamper generalization of our findings to the general migraine population. In accordance with previous studies,[2,3,5]we found that migraine patients had higher WML volume load compared to controls, albeit this did not reach statistical significance. This is likely because of limited statistical power and, in addition, the older age and high cardiovascular disease burden of our study population may have obscured migraine effects. We only assessed migraine diagnosis and no other headaches. Consequently, we were not able to assess whether the found association of endothelial shear stress with WMLs was specific for migraine or whether this was also present for other types of headache, as was suggested in a previous study.[37] Although the differences between females and males in our study highlight that sex-differences possibly play a role in the pathophysiology of migraine, it must be stated that our sample size is likely too small for a proper analysis of male migraine patients ($n = 11$), also visualized by the broad confidence intervals of the associations (Figure 3). Moreover, our sample size was too small to evaluate migraine with and without aura as separate groups.

In conclusion, we showed that migraine patients were associated with decreased carotid artery endothelial shear stress when compared to migraine-free controls and that migraine patients with lower carotid artery endothelial shear stress were associated with higher WML volumes. This reduced carotid artery endothelial shear stress may predispose patients with migraine to development of WMLs. Elucidating the relationship between endothelial shear stress and WMLs may lead to a better understanding of the pathophysiologic mechanism underlying the increased risk of WMLs in migraine patients.

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Declaration of conflicting interests

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Authors' contributions

Evelien S Hoogeveen analysed and interpreted the data and drafted/revised the manuscript.
Enrico B Arkink contributed to the analysis and interpretation of the data and revised the manuscript.
Jeroen van der Grond contributed to the analysis and interpretation of the data and revised the manuscript.
Mark A van Buchem designed the study and revised the manuscript.
Michel D Ferrari contributed to the analysis and interpretation of the data and revised the manuscript.
Gisela M Terwindt designed the study and revised the manuscript.
Mark C Kruit designed the study, contributed to the analysis and interpretation of the data and revised the manuscript.

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