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Prevalence of fascicular hyperintensities in peripheral nerves of healthy individuals with regard to cerebral white matter lesions

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Abstract

Objective Detection and pattern analysis of fascicular nerve hyperintensities in the T2-weighted image are the backbone of magnetic resonance neurography (MRN) as they may represent lesions of various etiologies. The aim of this study was to assess the prevalence of fascicular nerve hyperintensities in healthy individuals with regard to a potential association with age or cerebral white matter lesions.

Methods Sixty volunteers without peripheral nerve diseases between the age of 20 and 80 underwent MRN (high-resolution T2-weighted) of upper (median, ulnar, radial) and lower (sciatic, tibial) extremity nerves and a fluid-attenuated inversion recovery (FLAIR) sequence of the brain. Presence of peripheral nerve hyperintensities and degree of cerebral white matter lesions were independently rated by two blinded readers and related to each other and to age. *T* test with Welch's correction was used for group comparisons. Spearman's correlation coefficients were reported for correlation analyses.

Results MR neurography revealed fascicular hyperintensities in 10 of 60 subjects (16.7%). Most frequently, they occurred in the sciatic nerve (8/60 subjects, 13.3%), less frequently in the tibial nerve at the lower leg and the median, ulnar, and radial nerves at the upper arm (1.7–5.0%). Mean age of subjects with nerve hyperintensities was higher than that of those without (60.6 years vs. 48.0 years, $p = 0.038$). There was only a weak correlation of nerve lesions with age and with cerebral white matter lesions, respectively.

Conclusion Fascicular nerve hyperintensities may occur in healthy individuals and should therefore always be regarded in conjunction with the clinical context.

Key Points

- *MR neurography may reveal fascicular hyperintensities in peripheral nerves of healthy individuals. Fascicular hyperintensities occur predominantly in the sciatic nerve and older individuals.*
- *Therefore, fascicular hyperintensities should only be interpreted as clearly pathologic in conjunction with the clinical context.*

Keywords Healthy volunteers · Peripheral nerves · Magnetic resonance imaging

Abbreviations

DWMH	Deep white matter hyperintensitites
FLAIR	Fluid-attenuated inversion recovery
FOV	Field of view
MRN	Magnetic resonance neurography
PVH	Periventricular hyperintensities
SD	Standard deviation
T2w	T2-weighted
TE	Echo time
TI	Inversion time
TR	Repetition time
TSE	Turbo spin echo

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Introduction

Magnetic resonance neurography (MRN) applies dedicated MR sequences for imaging of peripheral nerves [1, 2]. While the potential of quantitative MRI techniques such as diffusion tensor imaging, perfusion imaging, or T2-relaxometry is being investigated in numerous studies [3–10], MRN in a current clinical setting primarily relies on morphologic criteria and signal alterations, in particular on the detection of pathologic fascicular lesions, which appear as hyperintensities in high-resolution T2-weighted (T2w) fat-suppressed sequences [1, 2, 11]. These hyperintensities are a common, yet unspecific feature of various neuropathies of different etiologies, such as inflammatory, metabolic, hereditary, traumatic, or compressive neuropathies [5, 12–16]. Analysis of the distribution pattern of nerve lesions in conjunction with the clinical history is often the key to the final diagnosis [2, 17].

In the current literature, the typical appearance of a normal nerve in MR neurography is described as isointense or only slightly hyperintense in the T2-weighted image, when compared with the adjacent muscular tissue [1, 18, 19]. Only in typical sites of compression asymptomatic peripheral nerve hyperintensities have been reported [20].

In contrast to the peripheral nervous system, where a T2w hyperintense lesion in a nerve is usually regarded as pathological, T2w hyperintense white matter lesions in the central nervous system have extensively been described in asymptomatic individuals [21–23]. In the elderly, they are often interpreted as a correlate of small vessel disease [24], but when only mild, they may reflect normal ageing [25].

While many studies have sought to assess the prevalence and pathological significance of white matter lesions in the brain [21–23, 26, 27], we are not aware of a study that similarly assessed the possible prevalence of peripheral nerve hyperintensities in healthy individuals.

The aim of this study was to assess the prevalence of fascicular hyperintensities in peripheral nerves in healthy individuals with particular regard to a possible association with age or cerebral white matter lesions.

Methods

Subjects

This prospective study was approved by the institutional ethics committee. It was conducted in accordance with the Declaration of Helsinki and all participants gave written informed consent. Sixty healthy participants (30 men and 30 women) between the age of 20 and 80 were recruited evenly throughout all age decades (5 men and 5 women per decade). Demographic characteristics of the study group and association of demographic variables with nerve cross-sectional area have been published separately [3]. Inclusion criteria were age between 20 and 80 years; exclusion criteria were known peripheral or central neurological diseases as well as inflammatory or metabolic systemic diseases (e.g., diabetes mellitus) and history of cancer as well as general contraindications for MRI.

Magnetic resonance neurography

All examinations were conducted at 3.0 T on a Magnetom Tim-Trio (Siemens Healthineers). MRN of upper and lower extremity nerves was acquired as previously described [3, 5] by three slabs at (1) mid–upper arm, (2) mid-thigh, and (3) proximal lower leg of a randomly selected side of a high-resolution T2-weighted turbo spin echo (TSE) sequence with the following parameters: repetition time (TR) = 7000 ms, echo time (TE) = 55 ms, 2 excitations, axial orientation, slice thickness = 3.5 mm, interslice gap = 0.35 mm, field of view (FOV) 160 × 160 mm^2, matrix size = 512 × 333, 41 slices, acquisition time per slab 3 min 46 s. A 16-channel receive-only flex coil was used for slab 1 (Variety, Noras MRI Products) and a 15-channel transmit-receive knee coil (Siemens Healthineers) for slabs 2 and 3.

Additionally, MRI of the brain was performed acquiring a standard axial fluid-attenuated inversion recovery (FLAIR) sequence with the following parameters: TR = 10,000 ms, TE = 96 ms, inversion time (TI) = 2500 ms, 1 excitation, slice thickness = 5 mm, interslice gap 0.5 mm, FOV 200 × 230 mm^2, matrix 256 × 224, acquisition time per slab 2 min 42 s. Cerebral imaging was performed with a 32-channel head coil (Siemens Healthineers).

Blinded reading

All images were blinded with respect to age, sex, and any personal information. Two readers (M.K. and P.B.) with more than 4 and 9 years of experience in neuromuscular imaging independently rated presence or absence of T2w hyperintense fascicular nerve lesions in MRN images in the sciatic nerve at the thigh, the tibial nerve at the lower leg, and the median, ulnar, and radial nerves at the upper arm. Hyperintensities that could clearly be recognized as intraneural vessels [28] or artefacts were not taken into account. Areas known to be particularly prone to magic angle artefact were not evaluated in this study [29, 30]. Nerves were only evaluated outside typical locations of nerve compression. Therefore, the ulnar sulcus (cubital tunnel) was excluded from reading. Moreover, soft tissue surrounding the nerves was evaluated as a possible cause of nerve compression that might be potentially caused by vessels [31] or other compressive structures. Images were excluded from the analysis if image quality was rated insufficient by at least one reader as indicated in Table 1. Consensus of nerve lesion rating was defined conservatively, such that fascicular hyperintensities were only counted as present if both readers independently recognized a lesion.

Table 1 Results of nerve hyperintensity rating—consensus. Percentage and fraction of subjects, in which fascicular nerve hyperintensities were detected. Consensus was defined conservatively such that hyperintensities were only counted if both readers independently rated those

	Fascicular hyperintensities		No hyperintensities		Excluded	
Sciatic nerve	13.3%	8/60	86.7%	52/60	0%	0/60
Tibial nerve	1.7%	1/60	96.7%	58/60	1.7%	1/60
Ulnar nerve	5.0%	3/60	93.3%	56/60	1.7%	1/60
Median nerve	5.0%	3/60	91.7%	55/60	3.3%	2/60
Radial nerve	1.7%	1/60	93.3%	56/60	5.0%	3/60

Independently of nerve lesion rating, the readers assessed the degree of cerebral microangiopathy by grading periventricular hyperintensities (PVH) and deep white matter hyperintensities (DWMH) by a modified Fazekas score in the cerebral FLAIR image as follows: PVH: 0 = absence, 1 = "caps" or pencil-thin lining, 2a = smooth "halo" (mild), 2b = smooth "halo" (prominent), 3 = irregular hyperintensities; DWMH: 0 = absence, 1 = punctate foci, 2a = confluence of foci (mild), 2b = confluence of foci (moderate), 3 = large confluent areas. A modification to the original Fazekas score [32] was that grade 2 was divided into 2a and 2b. Image quality of FLAIR images was sufficient in all cases such that no data had to be excluded. Assessment of cerebral microangiopathy was performed independently and blinded of nerve lesion rating. Consensus of microangiopathy rating was defined as the minimum modified Fazekas score of both readers.

Statistical analysis

Statistical analysis was performed by M.K. using Prism Version 7, GraphPad Software, and SPSS Version 24, IBM. Cohen's kappa κ was calculated in order to assess interrater agreement for the assessment of nerve lesions (categorical variable). Weighted kappa κ_w with quadratic weights was determined to assess interrater agreement of cerebral white matter lesions by modified Fazekas score (ordinal variable). Spearman's rank correlation coefficient ρ was reported for all correlation analyses. A p value ≤ 0.05 was regarded as statistically significant. Due to the explorative character of the study, multiple testing was performed and the reported p values should be interpreted descriptively. T test with Welch's correction was used for group comparison in Supplementary Figs. 1 and 2. Independence of categorical variables (Supplementary Table 3) was assessed by chi-squared test.

Results

Subject characteristics

Sixty healthy subjects (30 men and 30 women) between 23 and 79 years were included in the study with 5 men and 5 women in each age decade. Mean age ± standard deviation (SD) was 50.1 ± 17.3 years. Detailed demographic characteristics of the study cohort are described in [3]. Six of the subjects were smokers with ≥ 2 pack-years and 6 subjects reported a pharmacologically treated hypertension.

Prevalence of fascicular nerve hyperintensities

In total, 10 of 60 subjects (16.7%) had hyperintensities in at least one nerve. Prevalence of fascicular nerve hyperintensities in single nerves as detected by consensus reading is presented in Table 1. Lesions were more frequent in the sciatic nerve (13.3%) than in all other nerves (1.7–5.0%). In all cases with lesions, MR images excluded nerve compression as a potential cause of the hyperintensities. Exemplary images of fascicular lesions in the sciatic nerve are presented in Fig. 1, those of lesions in upper extremity nerves in Fig. 2. Interrater agreement was $\kappa = 0.85$ for ulnar and median nerves, 0.59 for the sciatic nerve, and 0.21 and 0.19 for tibial and radial nerves, respectively. Results of independent nerve lesion grading for readers 1 and 2 are presented in Supplementary Tables 1 and 2.

Prevalence of cerebral microangiopathy and association with age

Results of microangiopathy scoring in the cerebral FLAIR image are presented in Table 2. Interrater agreement was $\kappa_w = 0.80$ for PVH and 0.85 for DWMH. The degree of cerebral microangiopathy was significantly associated with age (PVH: $\rho = 0.65$, $p \leq 0.0001$; DWMH: $\rho = 0.55$, $p \leq 0.0001$; Table 3).

Association of fascicular nerve hyperintensities with potential risk factors

On average, subjects with peripheral nerve hyperintensities were older than those without (60.6 years vs. 48.0 years, $p = 0.038$; Supplementary Fig. 1). In single nerve correlation analyses, this translated into only weak trends of association of age with presence of nerve lesions (Table 4 for consensus results, Supplementary Table 2 for single reader results).

Correlation analysis of peripheral nerve lesions with cerebral microangiopathy scoring similarly revealed only very weak, mostly positive trends that were only significant for the ulnar and median nerve (Table 4, Supplementary Table 2).

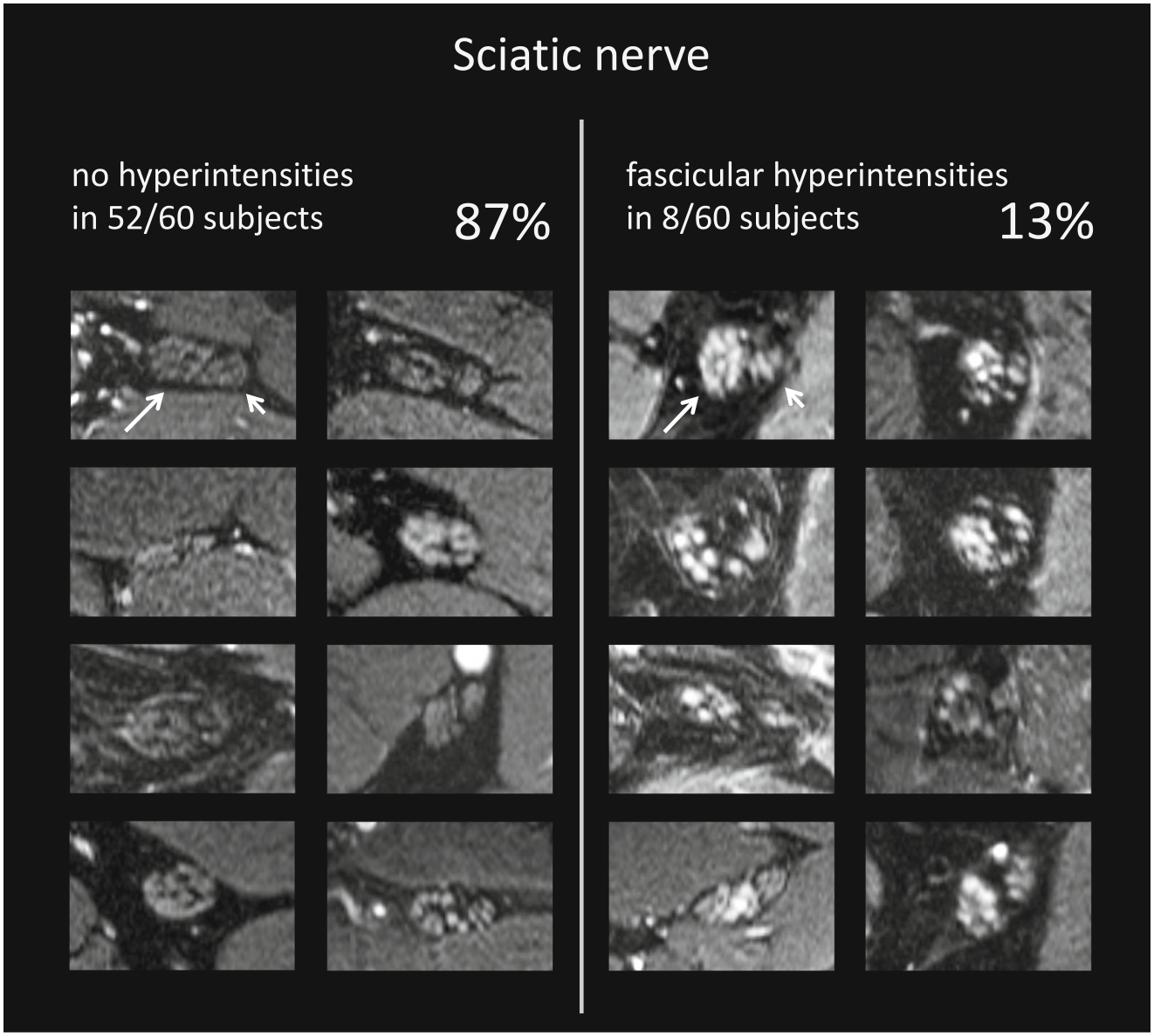

Fig. 1 Representative examples of sciatic nerve hyperintensities. Representative magnetic resonance neurography (MRN) images of sciatic nerves at thigh level of subjects with and without fascicular hyperintensitites (T2-weighted, fat-saturated). Long arrow = tibial portion, short arrow = peroneal portion

Body mass index of subjects with peripheral nerve hyperintensities did not significantly differ from those without (26.2 vs. 24.3 kg/m^2, $p = 0.298$, Supplementary Fig. 2). We further evaluated hypertension, smoking, and sex as potential risk factors (Supplementary Table 3). Of these, we found only hypertension to be more frequent in the group of the 10 subjects with fascicular hyperintensities ($p = 0.02$).

Discussion

In this study, we report the prevalence of fascicular hyperintensities in peripheral nerves in a cohort of 60 healthy individuals. Using correlation analysis, we evaluated a possible association with age and cerebral white matter hyperintensities in the context of cerebral microangiopathy. This study represents the first systematic description of true fascicular nerve hyperintensities in healthy individuals offside common nerve entrapment sites.

We found fascicular hyperintensities in 17% of the examined healthy subjects. Most frequently, they occurred in the sciatic nerve. In the current literature, a normal nerve in the T2-weighted image is characterized as isointense or only slightly hyperintense to the bordering muscles [1, 18, 19]. Concerning the ulnar nerve, hyperintensities have been reported in healthy individuals at the elbow, a common site of nerve compression

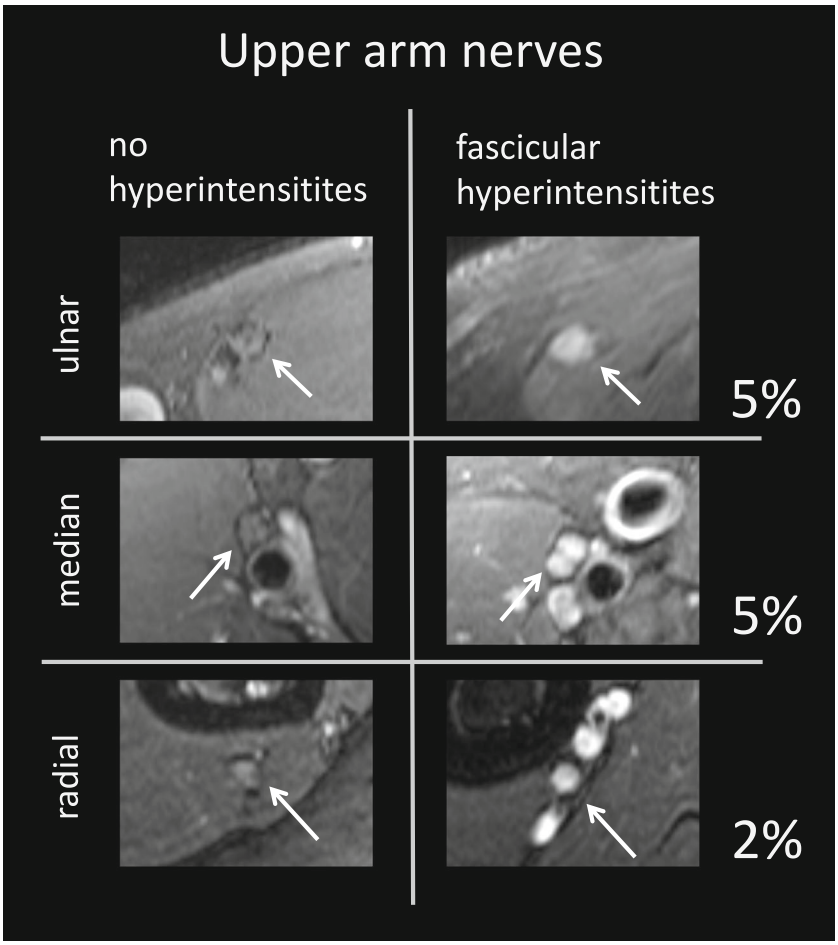

Fig. 2 Representative examples of upper arm nerve hyperintensities. Representative magnetic resonance neurography (MRN) images of upper arm nerves of subjects with and without peripheral nerve hyperintensities (T2-weighted, fat-saturated). Numbers indicate percentages of subjects with hyperintensities

[20]. Outside the typical locations of nerve compression, fascicular hyperintensities have usually been regarded as pathologic and have been described in peripheral neuropathies of various etiologies such as compressive, metabolic, inflammatory, hereditary, or traumatic neuropathies [5, 12–16]. Our study for the first time reports true fascicular hyperintensities in individuals without diseases of peripheral nerve.

As MR neurography examinations are frequently performed in cases of neurologic symptoms of unclear etiology and may channel further treatment, it is highly relevant to not over- or under-interpret imaging findings. The detection of fascicular hyperintensities in healthy individuals should therefore prompt careful interpretation of fascicular nerve lesions taking into account other additional, morphological findings like nerve cross-

Table 2 Results of cerebral white matter lesion scoring. Periventricular hyperintensities (PVH) and deep white matter hyperintensities (DWMH) in the cerebral FLAIR image were rated separately according to a modified Fazekas score: PVH: 0 = absence, 1 = "caps" or pencil-thin lining, 2a = smooth "halo" (mild), 2b = smooth "halo" (prominent), 3 = irregular hyperintensities; DWMH: 0 = absence, 1 = punctate foci, 2a = confluence of foci (mild), 2b = confluence of foci (moderate), 3 = large confluent areas. Table shows the number of subjects in each score category. Consensus was defined conservatively as the minimum score of both readers

Modified Fazekas	Periventricular white matter			Deep white matter		
	Consensus	Reader 1	Reader 2	Consensus	Reader 1	Reader 2
0	40	28	36	40	40	30
1	10	20	13	10	10	13
2a	7	8	8	7	7	13
2b	1	1	1	2	2	3
3	2	3	2	1	1	1

Table 3 Correlation analyses of cerebral white matter lesions with age. Modified Fazekas score of deep white matter lesions and periventricular white matter lesions was correlated with age. Spearman's correlation coefficients ρ and respective p values are reported

	Consensus	Reader 1	Reader 2
Modified Fazekas (periventricular white matter) / age	$\rho = 0.654$ $p < 0.0001$*	$\rho = 0.570$ $p < 0.0001$*	$\rho = 0.634$ $p < 0.0001$*
Modified Fazekas (deep white matter) / age	$\rho = 0.547$ $p < 0.0001$*	$\rho = 0.547$ $p < 0.0001$*	$\rho = 0.561$ $p < 0.0001$*

*$p \leq 0.05$

sectional area, the clinical history, and electrophysiological findings. This is particularly important when assessing the sciatic nerve at thigh level. Further studies and profound clinical experience may help to better define a cutoff where normality ends and where pathology starts. In other areas of radiology such as spinal imaging, the abundance of abnormal imaging findings in healthy individuals is much better investigated [33] and radiologists usually carefully interpret imaging findings in conjunction with the clinical history. We believe that a similar approach might be necessary in MR neurography. Besides, quantitative MRN techniques such as diffusion tensor imaging or T2 relaxometry might offer complementary information about the tissue composition and thus potentially help to differentiate between non-specific hyperintensities and true pathologic findings.

In contrast to peripheral nerves, white matter T2w hyperintensities in the central nervous system have been well characterized in healthy individuals. They are present in 95% of subjects above the age of 65, regarded as a correlate of small vessel disease and represent a risk factor for cerebrovascular events and cognitive decline in advanced stages [21, 23, 26, 27, 34].

In addition to investigating the prevalence of fascicular hyperintensities of peripheral nerve in healthy individuals, we also sought to address the question whether or not they represent the peripheral counterpart of cerebral white matter lesions—both reflecting small vessel disease.

Our study provides evidence that both processes share similar risk factors. The correlation of cerebral white matter lesions with age is well established in the literature [26, 27] and corroborated by our findings (Table 3). While correlation analysis of peripheral nerve lesions with age was less clear-cut, it likewise revealed positive trends for all nerves (Table 4). Moreover, mean age of subjects with nerve lesions was higher than that of subjects without lesions and the majority of subjects with lesions were older than 60 years (Supplementary Fig. 1). As hypertension has been reported as a risk factor for cerebral white matter lesions [22, 27], this was also over-represented in the subjects with peripheral nerve lesions, albeit this finding has to be interpreted with care due to the low absolute number of included subjects with hypertension (Supplementary Table 3).

While the above findings provide some evidence that cerebral white matter lesions and peripheral nerve hyperintensities share similar risk factors, direct correlation analysis between peripheral nerve lesions and the degree of cerebral microangiopathy only revealed weak positive trends (Table 4).

Development of cerebral white matter lesions results from a complex interplay of multiple pathophysiological processes, which is so far poorly understood [35, 36]. What is the histological correlate of peripheral nerve hyperintensities in healthy volunteers? Animal models of peripheral nerve injury suggest that T2w hyperintensities in injured peripheral nerves represent

Table 4 Correlation analyses of nerve hyperintensity rating with age and cerebral white matter lesions. All analyses refer to results of consensus reading. Spearman's correlation coefficients ρ and the respective p values are presented

		Age	Modified Fazekas periventricular white matter	Modified Fazekas deep white matter
Nerve hyperintensity rating	Sciatic nerve	$\rho = 0.215$ $p = 0.098$	$\rho = 0.168$ $p = 0.200$	$\rho = 0.154$ $p = 0.239$
	Tibial nerve	$\rho = 0.131$ $p = 0.322$	$\rho = 0.219$ $p = 0.095$	$\rho = 0.215$ $p = 0.103$
	Ulnar nerve	$\rho = 0.299$ $p = 0.021$*	$\rho = 0.281$ $p = 0.031$*	$\rho = 0.333$ $p = 0.010$*
	Median nerve	$\rho = 0.310$ $p = 0.018$*	$\rho = 0.288$ $p = 0.028$*	$\rho = 0.341$ $p = 0.009$*
	Radial nerve	$\rho = 0.012$ $p = 0.928$	$\rho = -0.089$ $p = 0.510$	$\rho = -0.086$ $p = 0.527$

*$p \leq 0.05$

myelin loss, axonal loss, distortion of axoplasmatic flow, and widening of the extracellular space [19, 37–39]. Histological correlation in healthy volunteers is not feasible, so we can only speculate which phenomena might underlie the observed hyperintensities in our cohort. Since microangiopathical changes are known to also affect peripheral nerves [40], we put forward the hypothesis that fascicular hyperintensities in peripheral nerves might represent a correlate of microangiopathy, similar to cerebral white matter lesions.

However, we did not find a convincing association of fascicular hyperintensities in peripheral nerves with cerebral white matter lesions. This rather implies that they cannot simply be regarded as a counterpart of each other. While they share age and arterial hypertension as common risk factors, our results support the notion that their pathophysiology differs, at least to some extent.

Our study has several limitations. While the total number of subjects in this study is in the usual range of MR neurography studies, the number of subjects with peripheral nerve hyperintensities is low. Therefore, all correlation analyses should be interpreted carefully. This particularly applies to correlation with cerebral microangiopathy, since in our impression white matter lesions in our cohort of healthy volunteers were less severe than in average patients with clinical imaging indications. Further studies specifically recruiting subjects with prominent white matter lesions or vascular risk factors would be desirable. Moreover, we excluded peripheral nerve diseases by clinical history only and therefore cannot completely rule out that some individuals might have had clinically occult neuropathies.

In summary, we found fascicular hyperintensities in peripheral nerves of 17% of healthy subjects. They were most common in the sciatic nerve and tended to predominantly occur in older subjects. While our study provides some evidence that peripheral nerve lesions and cerebral white matter lesions might share common risk factors, they are not correlated with each other and may be considered separate pathophysiological processes. In conclusion, fascicular nerve hyperintensities may occur in healthy individuals and should therefore always be regarded in conjunction with the clinical context.

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Compliance with ethical standards

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Conflict of interest The authors of this manuscript declare no relationships with any companies whose products or services may be related to the subject matter of the article.

Statistics and biometry No complex statistical methods were necessary for this paper.

Informed consent Written informed consent was obtained from all subjects (patients) in this study.

Ethical approval Institutional Review Board approval was obtained.

Study subjects or cohorts overlap Diffusion tensor imaging, T2-relaxometry and nerve cross sectional area data of the same cohort have been published separately:

1. Kronlage M, Schwehr V, Schwarz D et al (2017) Magnetic Resonance Neurography: Normal Values and Demographic Determinants of Nerve Caliber and T2 Relaxometry in 60 healthy individuals. Clinical Neuroradiology. https://doi.org/10.1007/s00062-017-0633-5
2. Kronlage M, Schwehr V, Schwarz D et al (2018) Peripheral nerve diffusion tensor imaging (DTI): normal values and demographic determinants in a cohort of 60 healthy individuals. European Radiology 28:1801–1808

18 of 60 subjects were used in a control group for:

1. Kronlage M, Bäumer P, Pitarokoili K et al (2017) Large coverage MR neurography in CIDP: diagnostic accuracy and electrophysiological correlation. Journal of Neurology 264:1434–1443
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Methodology
- prospective
- cross sectional study
- performed at one institution

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