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ABSTRACT

BACKGROUND AND PURPOSE: Spinal cord atrophy is a common and clinically relevant characteristic in multiple sclerosis. We aimed to perform a multicenter validation study of mean upper cervical cord area measurements in patients with multiple sclerosis and healthy controls from head MR images and to explore the effect of gadolinium administration on mean upper cervical cord area measurements.

MATERIALS AND METHODS: We recruited 97 subjects from 3 centers, including 60 patients with multiple sclerosis of different disease types and 37 healthy controls. Both cervical cord and head 3D T1-weighted images were acquired. In 11 additional patients from 1 center, head images before and after gadolinium administration and cervical cord images after gadolinium administration were acquired. The mean upper cervical cord area was compared between cervical cord and head images by using intraclass correlation coefficients (ICC) for both consistency (ICC_{consist}) and absolute (ICC_{abs}) agreement.

RESULTS: There was excellent agreement of mean upper cervical cord area measurements from head and cervical cord images in the entire group ($ICC_{\text{abs}} = 0.987$) and across centers and disease subtypes. The mean absolute difference between the mean upper cervical cord area measured from head and cervical cord images was 2 mm^2 (2.3%). Additionally, excellent agreement was found between the mean upper cervical cord area measured from head images with and without gadolinium administration ($ICC_{\text{abs}} = 0.991$) and between the cervical cord and head images with gadolinium administration ($ICC_{\text{abs}} = 0.992$).

CONCLUSIONS: Excellent agreement between mean upper cervical cord area measurements on head and cervical cord images was observed in this multicenter study, implying that upper cervical cord atrophy can be reliably measured from head images. Postgadolinium head or cervical cord images may also be suitable for measuring mean upper cervical cord area.

ABBREVIATIONS: EDSS = Expanded Disability Status Scale; Gd = gadolinium; HC = healthy control; ICC = intraclass correlation coefficient; ICC_{abs} = ICC absolute agreement; ICC_{consist} = ICC consistency; MUCCA = mean upper cervical cord area; PPMS = primary-progressive MS; RRMS = relapsing-remitting MS, SPMS = secondary-progressive MS

Spinal cord atrophy is recognized as a common and clinically relevant characteristic in patients with multiple sclerosis.¹ Differences in cervical cord volume and area among patients

with different phenotypes of MS and healthy controls (HCs) measured by MR imaging have been identified in many studies.²⁻⁴ Furthermore, a modest or strong correlation between spinal cord atrophy and disability has been demonstrated in

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numerous studies, suggesting that spinal cord atrophy is an essential determinant of clinical disability and a potential outcome measure to monitor MS disease progression.⁵⁻⁷ The measurement of the upper cervical cord area is a well-established method for the assessment of spinal cord atrophy and has been applied in most studies so far.^{2,3,5,8,9} Both image acquisition and spinal cord segmentation are technically feasible and more accurate in the upper cervical region compared with other parts of the cord or the entire cord.¹⁰ In addition, the upper cervical cord is more frequently affected by MS pathology than lower parts of the spinal cord.¹¹

Mean upper cervical cord area (MUCCA) can be measured by using 3D T1-weighted MR images of the cervical cord.^{3,4} The MUCCA also has been measured recently on 3D T1-weighted MR images of the head covering the upper cervical cord, which has yielded promising results showing associations between MUCCA and clinical disability and disease progression.^{2,5} Measuring the MUCCA from head MR images offers the opportunity to analyze MUCCA retrospectively in datasets without dedicated cervical 3D T1-weighted images, and it can reduce costs and patient burden in prospective studies by eliminating the need for separate cervical cord image acquisitions if these are only acquired to measure the MUCCA. An MR imaging contrast agent is commonly used to detect the blood-brain barrier breakdown and inflammation in new lesions^{12,13} in patients with MS, which might influence the MUCCA measurements by tissue-contrast changes. The effect of the MR imaging contrast agent on MUCCA measurement also has to be investigated to ease the implementation of MUCCA as an auxiliary measurement in clinical practice. Although MUCCA measurements based on head 3D T1-weighted images have been successfully used in a monocenter study,¹⁴ multicenter validation is lacking. In addition, the possible effect of intravenous contrast administration on MUCCA measurements has not been investigated.

Therefore, the aim of the current study was to validate the measurement of the MUCCA on the basis of head compared with cervical cord 3D T1-weighted images in patients with MS and healthy controls on different MR imaging systems by using different acquisition parameters from multiple centers and to explore the effect of gadolinium (Gd) administration on MUCCA measurements.

MATERIALS AND METHODS

Subjects

The study was approved by the local institutional review board of the 3 centers (Amsterdam, Beijing and Bochum), and informed consent was obtained from each participant.

To investigate the variability of the MUCCA based on head 3D T1 MR images and cervical cord 3D T1 MR images, we selected scans from ongoing local cohorts in which separate head and cervical cord 3D T1 MR images were acquired. All images were checked for visibility of the spinal cord without artifacts, and head images were checked for coverage of the upper cervical cord. A total of 97 subjects were recruited from 3 centers (A: Amsterdam, B: Beijing, and C: Bochum), including 40 patients with relapsing-remitting MS (RRMS), 10 with

Table 1: Scan protocols for all 3 centers^a

	Center A (n = 58)	Center B (n = 28)	Center C (n = 7)
Vendor	GE Healthcare ^b	Siemens ^c	Philips Healthcare ^d
Scanner	Signa HDxt	Trio Tim	Achieva
Head MRI			
Sequence	FSPGR	MPRAGE	FFE
No. of sections	176	176	180
TR (ms)	7.8	1600	10
TE (ms)	3	2.13	4.6
T1 (ms)	450	1000	1000
FA	12°	9°	8°
Voxel size (mm)	0.94 × 0.94 × 1	1 × 1 × 1	1 × 1 × 1
Cervical MRI			
Sequence	FSPGR	MPRAGE	FFE
No. of sections	176	96	64
TR (ms)	7.3	2000	8
TE (ms)	3	3.36	3.5
T1 (ms)	450	1100	1000
FA	15°	10°	8°
Voxel size (mm)	1 × 1 × 1	1 × 1 × 1	1 × 1 × 1

Note:—FA indicates flip angle; FFE, fast-field echo; FSPGR, fast spoiled gradient recalled.

^a All images had a sagittal orientation.

^b Milwaukee, Wisconsin.

^c Erlangen, Germany.

^d Best, the Netherlands.

primary-progressive MS (PPMS), 10 with secondary-progressive MS (SPMS), and 37 HCs. The subjects from the Amsterdam center were selected from a larger cohort (most data from this cohort have been published before³) in a semirandom fashion, to include 20 with RRMS, 10 with SPMS, 10 with PPMS, and 20 HCs. We ensured that the selected subsets spanned the range of spinal cord area of the total group (on the basis of the previously published measurements from cervical images³).

MS diagnosis was determined according to the 2010 revisions of the McDonald criteria.¹⁵ The main demographic and clinical characteristics included the Expanded Disability Status Scale (EDSS)¹⁶ scores and disease duration of the participants.

To explore the effect of intravenous Gd administration on MUCCA measurements, we included an additional 11 patients from Center C, including 2 with clinically isolated syndrome suggestive of MS and 9 with RRMS. In these patients, head images before and after Gd administration and cervical cord images after Gd administration were acquired.

MR Imaging Acquisition

In all 3 centers, a 3T MR imaging system was used to acquire high-resolution 3D sagittal T1-weighted head (with head coils) and cervical cord (with spine coils) images in the same scanning session. Corrections for geometric distortion due to gradient nonlinearity were applied in 3D. Details of MR imaging systems and acquisition parameters are provided in Table 1.

Image Analysis

Images were anonymized before MUCCA measurement and presented in a random order to the rater (Y.L., with >8 years of experience). MUCCA was defined as the average area of the 30-mm-length section of the upper cervical cord, starting at the upper borders of vertebral level C2, measured by using the

semiautomated software NeuroQLab (Fraunhofer MEVIS, Bremen, Germany) (Fig 1). In short, NeuroQLab segments the upper cervical cord from surrounding non-spinal cord tissue by using a Gaussian mixture modeling method. The workflow and the reliability of the software have been described previously.^{2,3,17,18}

Statistical Analysis

Analyses were performed by using SPSS software (Version 18; IBM, Armonk, New York). Kolmogorov-Smirnov tests were performed together with visual inspection of histograms to assess the normality of the variables. Comparison of the demographic data and MR imaging parameters between different disease subtypes and HCs or among different centers was conducted by using ANOVA, with Bonferroni correction for post hoc comparisons.

The intraclass correlation coefficients (ICCs) were calculated to assess both absolute agreement (ICC_{abs}) and consistency ($ICC_{consist}$) between MUCCA measurements from head and cervical cord images. These calculations were also performed separately for each center and each disease subtype. The difference between MUCCA measurements on head and cervical cord images was calculated in square millimeters and as percentages. For the exploratory analysis of the effects of intravenous Gd administration, the above-mentioned analyses were additionally performed in patients with MS from Center C included in that part of our study.

RESULTS

Demographics and Clinical and MR Imaging Characteristics

Five subjects were excluded from the final analysis, including 2 HCs from Center A (1 head scan and 1 cervical cord scan with artifacts) and 1 with RRMS, 1 HC from Center B (head scan with artifacts), and 1 patient with RRMS from Center C (the head scan without Gd administration did not cover the upper cervical cord). Finally, 103 subjects were left for final analysis, including 93 subjects without Gd administration from 3 centers (Table 2) and 10 patients with images before and after Gd administration from Center C. As shown in Table 2 and in line with the recruitment of long-standing patients with MS and matched healthy controls in Center A,³ the age of the subjects (including patients and HCs) was older in Center A than in the other 2 centers, and patients from center A had a longer average disease duration and higher EDSS scores than patients from Center B.

MUCCA measured from cervical cord images did not differ among centers in HCs (Center A: $81 \pm 9 \text{ mm}^2$, Center B: $80 \pm 6 \text{ mm}^2$, Center C: $84 \pm 10 \text{ mm}^2$, $F = 0.51$, $P = .61$). For the whole cohort, the MUCCA measured from cervical cord images in patients with MS was significantly lower than that in HCs ($P < .001$). Specifically, in patients with SPMS ($P = .02$) and PPMS ($P < .001$), the MUCCA was

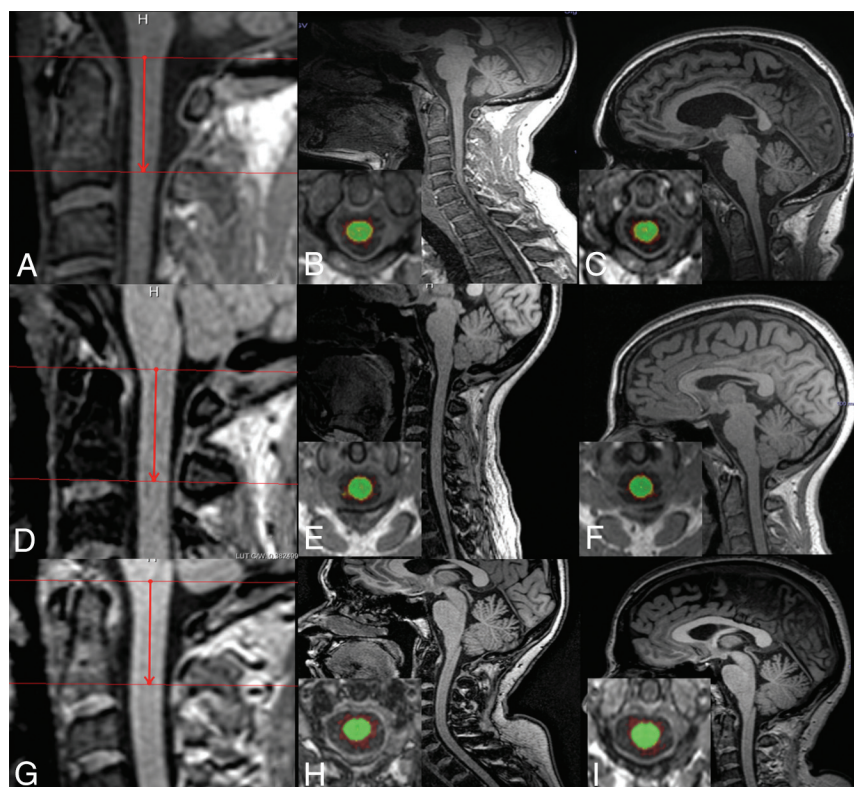


FIG 1. Examples of images from each center (cervical cord and head images). Sagittal T1-weighted MR image of the ROI selection (30-mm section length) in the upper cervical cord, starting at the upper borders of vertebral level C2 (A, D, and G), and sagittal images of the cervical cord and head with representative axial reformats overlaid by corresponding segmentation images from a patient with SPMS from Center A: B, MUCCA cervical cord images = 62 mm^2 , C, MUCCA head images = 64 mm^2 . A patient with RRMS from Center B: E, MUCCA cervical cord images = 74 mm^2 ; F, MUCCA head images = 75 mm^2 . An HC subject from Center C: H, MUCCA cervical cord images = 82 mm^2 ; I, MUCCA head images = 80 mm^2 .

Table 2: Demographic and clinical characteristics of subjects without Gd administration^a

	Center A (n = 58)				Center B (n = 28)		Center C (n = 7)
	RRMS (n = 20)	SPMS (n = 10)	PPMS (n = 10)	HC (n = 18)	RRMS (n = 19)	HC (n = 9)	HC (n = 7)
Sex (female/male)	12:8	4:6	5:5	11:7	13:6	6:3	5:2
Age (yr)	50.5 ± 8.4 (33–65)	63.4 ± 4.7 (54–70)	55.8 ± 4.6 (49–65)	51.9 ± 6.8 (36–61)	33.5 ± 8.7 (17–49)	32.4 ± 11.9 (21–56)	38.6 ± 11.8 (26–53)
Disease duration (yr)	18.8 ± 5.8 (9–29)	20.7 ± 7.6 (10–33)	19.5 ± 4.6 (12–27)	NA	4.3 ± 2.5 (1–10)	NA	NA
EDSS score	3.5 (2.5–6.5)	5 (3.5–8)	5.5 (3–7.5)	NA	3 (0–6.5)	NA	NA

Note:—NA indicates not applicable.

^aData are presented as mean \pm SD (range).

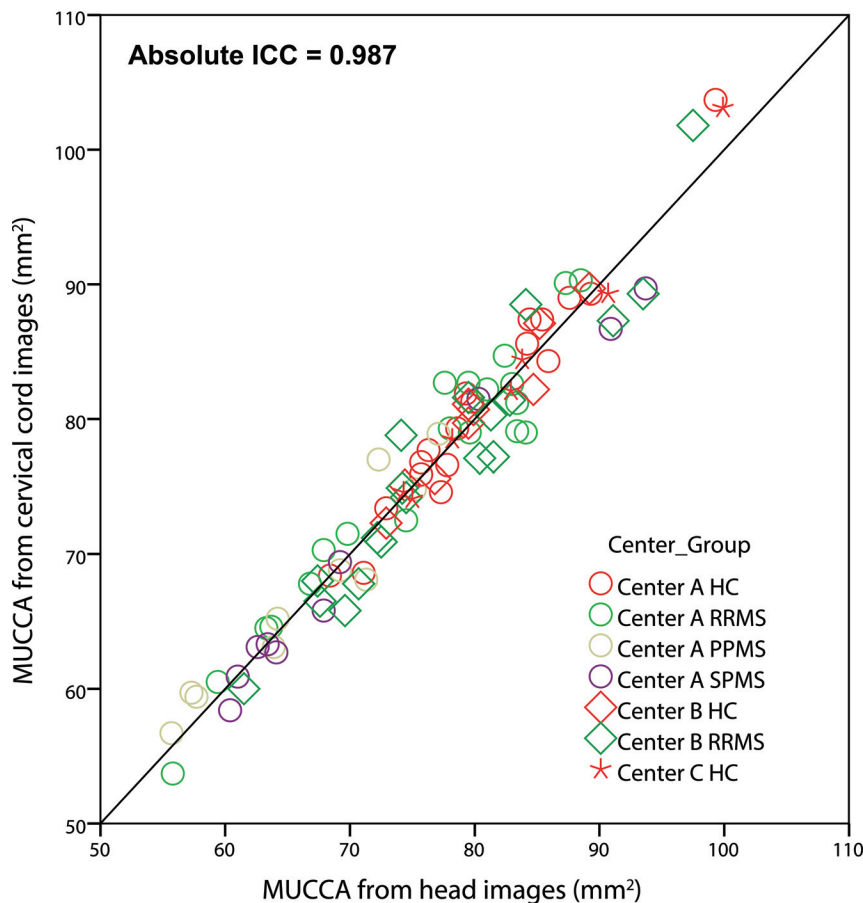


FIG 2. Scatterplot of the MUCCA measured from head-versus-cervical cord images. Different shapes indicate different centers (*circle*: Center A; *diamond*: Center B; *star*: Center C), and different colors represent different subgroups of subjects (red: HC; green: RRMS; yellow: PPMS; purple: SPMS). The solid black line indicates perfect agreement.

significantly smaller compared with HCs, and patients with PPMS showed smaller MUCCAs than those with RRMS ($P = .01$), whereas the MUCCA did not differ between patients with RRMS and HCs ($P = .20$) or between those with SPMS and those with RRMS ($P = .63$). MUCCA measured from head images showed similar group effects across centers and groups, including differences between those with MS and HCs, as well as among disease subtypes.

Concordance of MUCCA Measurements from Cervical Cord Images and Head Images

There was excellent absolute and consistency agreement of MUCCA measurements from head and cervical cord images in the whole group ($ICC_{abs} = 0.987$, $ICC_{consist} = 0.987$). Similarly, strong ICCs were observed across different centers and disease subtypes (On-line Table). The mean difference between MUCCA measured from head images and cervical cord images was 0.1 mm^2 (0.1%), ranging from -5 mm^2 (-6.1%) to 5 mm^2 (6.6%). The mean absolute difference was 2 mm^2 (2.3%), ranging from 0 to 5 mm^2 (6.6%) (On-line Table). For illustration purposes, scatterplots (Fig 2) and Bland-Altman plots (Fig 3) were created, which provide information on the interchangeability of the 2 measurements, by using MUCCAs from cervical cord images as the criterion standard.

The Effect of Gd Administration on MUCCA Measurements

Table 3 presents the results of the comparisons between MUCCA measurements based on 3D T1 MR images with and without Gd administration. Excellent agreement was found between MUCCA measurements on head images with and without Gd administration ($ICC_{abs} = 0.991$, $ICC_{consist} = 0.990$) and between MUCCA measurements on cervical cord images and head images with Gd enhancement ($ICC_{abs} = 0.992$, $ICC_{consist} = 0.992$).

DISCUSSION

The results of the current study demonstrate that MUCCA can be reliably measured by using head images covering the upper cervical cord in a multicenter setting across MS subtypes. Furthermore, our data suggest that Gd enhancement does not have a substantial influence on MUCCA measurements.

Upper cervical cord atrophy is regarded as an important biomarker correlating with clinical disability and predicting disease progression in MS.^{2,4,5} Measurement of MUCCA is commonly used for assessing upper spinal cord atrophy. In our study, MUCCA was measured by using semiautomated software, for which high intra- and interrater reproducibility has been observed for

MUCCA measurements either from head images³ or cervical cord images² in previous studies. Although the primary objective of the current study was to determine agreement between head and cervical images, it is reassuring that in our study, differences were found in MUCCAs among disease subtypes: Patients with PPMS and SPMS showed smaller MUCCAs compared with HCs, and patients with PPMS demonstrated smaller MUCCAs compared with those with RRMS, based on both cervical cord and head images. For Center A, MUCCA has been reported before for these subjects because they were part of a larger cohort; in that study, MUCCA was measured independently by another rater than the one performing the measurements in the current study.³ These current findings are in line with previous studies showing that cervical cord atrophy is more pronounced in progressive subtypes.^{2,4}

Some previous studies have used head images to measure cervical cord atrophy,^{2,5,8,9} and a viable method is measuring the MUCCA. However, for MUCCA measurements to be widely applied to head images, in particular in a clinical trial setting, validation in a multicenter setting is necessary. Our study showed an average absolute difference in MUCCA between cervical cord and head images of <4%, and ICCs for absolute agreement ≥ 0.978 across centers and disease subtypes, which is consistent with a previous study from a single center showing an ICC > 0.95 be-

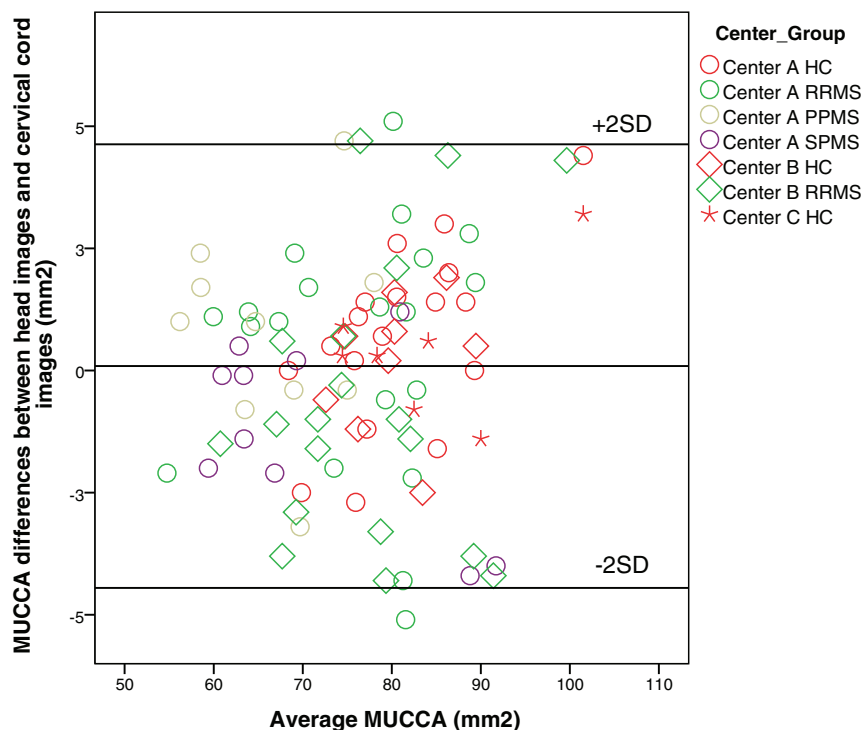


FIG 3. Bland-Altman plots for MUCCA measurements from cervical cord images and head images. The averages of MUCCA measurements on cervical cord and head images are shown on the horizontal axis, and the differences in MUCCA between the 2 measurements are shown on the vertical axis. Different shapes indicate different centers (*circle*: Center A; *diamond*: Center B; *star*: Center C), and different colors represent different subgroups of subjects (red: HC; green: RRMS; yellow: PPMS; purple: SPMS).

Table 3: Demographic and clinical characteristics of patients with Gd administration from Center C and comparison between MUCCA from nonenhanced head images, enhanced cervical cord and head images^a

Center C (8 RRMS + 2 CIS)	
Sex (female/male)	6:4
Age (yr)	39.0 ± 10.8 (29–67)
Disease duration (yr)	1.2 ± 1.2 (0.1–2.9)
EDSS score	2.6 ± 1.7 (1–5.5)
Gd+ MUCCA (cervical cord images) (mm ²)	82 ± 10 (67–96)
Gd– MUCCA (head images) (mm ²)	82 ± 10 (66–99)
Gd+ MUCCA (head images) (mm ²)	82 ± 10 (66–99)
Gd+ MUCCA (head images) vs Gd+ MUCCA (cervical cord images)	
Difference (mm ²)	–0.17 ± 2.00 (–30–30)
% Difference	–0.28 ± 2.21 (–3.48–3.12)
Absolute difference (mm ²)	1.49 ± 1.25 (0–30)
% Absolute difference	1.71 ± 1.32 (0.48–3.48)
ICC _{consist}	0.990
ICC _{abs}	0.991
Gd+ MUCCA (head images) vs Gd– MUCCA (head images)	
Difference (mm ²)	–0.34 ± 1.89 (–2–4)
% Difference	–0.40 ± 2.05 (–2.61–4.42)
Absolute difference (mm ²)	1.36 ± 1.29 (0–4)
% Absolute difference	1.53 ± 1.34 (0.14–4.42)
ICC _{consist}	0.992
ICC _{abs}	0.992

Note:—CIS indicates clinically isolated syndrome.

^aData are presented as mean ± SD (range).

tween MUCCA measurements from head and cervical cord images in patients with RRMS.¹⁴ The excellent agreement between MUCCA measurements using cervical cord and head images without systematic shift indicates that measuring the upper cervical cord area is feasible by using head MR imaging datasets if

they cover the upper cervical cord and if gradient inhomogeneity correction is applied in 3D. Retrospective studies can thus be performed in large MS data bases investigating upper cervical cord atrophy by using head images, which may help to improve our understanding of the role of spinal cord atrophy in MS. For future studies, upper cervical cord atrophy is an accessible outcome measure in treatment trials and clinical research without additional cervical cord image acquisitions, thus providing additional information without increasing image acquisition cost or patient burden.¹⁹

Gd administration is often included in routine MR imaging protocols of patients with MS²⁰ and can change the contrast of brain and spinal cord images. The question of whether the MUCCA can be reliably measured on images obtained after Gd administration is therefore clinically relevant, but it has not been investigated before, to our knowledge. In the current study, we were unable to perform a rigorous assessment with available data for only 10 patients from a single center. However, these preliminary results showed excellent

agreement of the MUCCA between head images with or without Gd administration and between head and cervical cord images with Gd administration, suggesting that Gd administration has little effect on MUCCA measurement. These results should be confirmed in a larger group of patients and a multiscanner setting. If future studies confirm the current finding, one could use head images or cervical cord images after Gd administration to measure MUCCA, which would present another option to assess cervical cord atrophy. However, care should be taken in case of enhancing intramedullary cervical cord lesions that may affect MUCCA estimation on images obtained after Gd administration. Because in the present study no enhancing lesions were observed on the postcontrast images, we cannot exclude a bias in such cases. Furthermore, enhanced spinal nerves after Gd administration may influence the segmentation of the cord, another potential factor influencing MUCCA measurement.

Although this study included only 3 centers, the 3 main MR imaging vendors and the most commonly used sequences for high-resolution cervical cord and head imaging were included. Despite the (subtle) differences in tissue contrast among different scanners and 3D T1 sequences, agreement was excellent, suggesting the generalizability of our results beyond scanners and pulse sequences. Therefore the MUCCA has the potential to become a viable marker for MS in a routine clinical setting and clinical treatment trials.

Several limitations apply to this work. First, we did not normalize the MUCCA measurements for intracranial volume, body height, or other parameters because optimal parameters for cer-

vical cord volume or area normalization remain controversial.^{21–23} Second, the presence of cord lesions including T2 hyperintensity and T1 hypointensity in the measurement area may influence MUCCA measurements due to underestimation of white matter volumes owing to lesion misclassification.⁹ However, the lesions are present on both cervical cord and head images, which may cause a similar effect on MUCCA measurements. The high ICC values in all subgroups suggest that if an effect is present, it is comparable between both image types. Third, HCs were younger than those with MS, especially those with SPMS and PPMS in Center A in the current study. High ICC values were identified in HCs and all MS subgroups, suggesting that age has little influence on the consistency of measurements of the MUCCA between cervical cord and head images. Finally, this is a cross-sectional study; a longitudinal study is warranted to extrapolate the current findings to MUCCA changes with time.

CONCLUSIONS

Excellent agreement between MUCCA measurements from cervical cord and head images was observed across centers and disease subtypes in a multicenter setting, implying that upper cervical cord atrophy can be reliably measured by using head images covering the upper cervical cord. If there are no enhancing cervical cord lesions, postcontrast 3D T1-weighted images of the cervical cord or head may also be a suitable source for measuring MUCCA. These findings have important implications for clinical studies, including treatment trials.

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