European Radiology
https://doi.org/10.1007/s00330-020-07521-1

MAGNETIC RESONANCE

Magnetic resonance T1w/T2w ratio in the middle cerebellar peduncle might be a sensitive biomarker for multiple system atrophy

Atsuhiko Sugiyama[1] · Hajime Yokota[2] · Shigeki Hirano[1] · Graham Cooper[3,4,5,6] · Hiroki Mukai[2] · Kyosuke Koide[1] · Jiaqi Wang[1] · Shoichi Ito[1,7] · Carsten Finke[5,8,9] · Alexander U Brandt[4,10] · Friedemann Paul[3,4,5,8] · Satoshi Kuwabara[1]

Received: 11 June 2020 / Revised: 10 October 2020 / Accepted: 13 November 2020

Abstract

Objective We aimed to investigate the use of a myelin-sensitive MRI contrast, the standardized T1-weighted/T2-weighted (sT1w/T2w) ratio, for detecting early changes in the middle cerebellar peduncle (MCP) in cerebellar subtype multiple system atrophy (MSA-C) patients.

Methods We included 28 MSA-C patients, including a subset of 17 MSA-C patients within 2 years of disease onset (early MSA-C), and 28 matched healthy controls. T1w and T2w scans were acquired using a 3-T MR system. The sT1w/T2w ratio in MCP was analyzed using SPM12 by utilizing a region-of-interest approach in normalized space. The diagnostic performance of the MCP sT1w/T2w ratio in discriminating MSA-C and the subgroup of early MSA-C from the matched controls was assessed. Correlation analyses were performed to evaluate the relationship between the MCP sT1w/T2w ratio and other clinical parameters including the International Cooperative Ataxia Scale (ICARS) score for quantifying cerebellar ataxia.

Results Compared to controls, the sT1w/T2w ratio in the MCP was markedly lower in all ($p < 0.001$) MSA-C patients and 17 early ($p < 0.001$) MSA-C patients. The MCP sT1w/T2w ratio had high sensitivity (96%) and specificity (100%) to distinguish MSA-C from controls (area under the curve = 0.99), even for the early MSA-C group (area under the curve = 0.99; sensitivity = 94%, specificity = 100%). The MCP sT1w/T2w ratio correlated with the ICARS score in early MSA-C.

Conclusions The sT1w/T2w ratio can detect MSA-C-related changes in the MCP, even in the early stages of the disorder, and could be a sensitive biomarker for MSA-C.

Key Points

- *The sT1w/T2w ratio can detect MSA-C-related changes in the middle cerebellar peduncle, even in the early stages of the disorder.*
- *The middle cerebellar peduncle sT1w/T2w ratio correlated with a cerebellar ataxia score in early MSA-C patients.*

Keywords Magnetic resonance imaging · Cerebellar ataxia · Middle cerebellar peduncle · Multiple system atrophy

✉ Atsuhiko Sugiyama
chinneosyo0624@yahoo.co.jp

[1] Department of Neurology, Graduate School of Medicine, Chiba University 1-8-1 Inohana, Chuo-ku, Chiba 260-8677, Japan

[2] Department of Diagnostic Radiology and Radiation Oncology, Graduate School of Medicine, Chiba University, Chiba, Japan

[3] Experimental and Clinical Research Center, Max Delbrueck Center for Molecular Medicine and Charité-Universitätsmedizin Berlin, corporate member of Freie Universität Berlin, Humboldt-Universität zu Berlin and Berlin Institute of Health, Berlin, Germany

[4] NeuroCure Clinical Research Center, Charité-Universitätsmedizin Berlin, Berlin, Germany

[5] Einstein Center for Neurosciences, Berlin, Germany

[6] Department of Experimental Neurology and Center for Stroke Research, Berlin, Charité – Universitätsmedizin Berlin, Berlin, Germany

[7] Department of Medical Education, Graduate School of Medicine, Chiba University, Chiba, Japan

[8] Department of Neurology, Charité-Universitätsmedizin Berlin, Berlin, Germany

[9] Berlin School of Mind and Brain, Humboldt-Universität zu Berlin, Berlin, Germany

[10] Department of Neurology, University of California, Irvine, CA, USA

Published online: 25 November 2020

Abbreviations

ICARS	International Cooperative Ataxia Rating Scale
MCP	Middle cerebellar peduncle
MSA-C	Cerebellar subtype multiple system atrophy
ROC	Receiver operating characteristic
SARA	Scale for the Assessment and Rating of Ataxia
sT1w/T2w	Standardized T1-weighted/T2-weighted
UMSARS	Unified Multiple System Atrophy Rating Scale

Introduction

Multiple system atrophy (MSA) is a progressive neurodegenerative disorder characterized by a combination of autonomic failure, cerebellar ataxia, parkinsonism, and pyramidal signs. The estimated prevalence is 1.9–4.9%. MSA is an incurable disease, resulting in death typically between 7 and 9 years after initial clinical presentation [1]. Symptomatic therapies are of limited use, with no effective neuroprotective therapy available so far. Therefore, developing good diagnostic tools in the early disease stage and objective biomarkers of disease progression is essential for estimating disease prognosis and evaluating novel disease-modifying therapies in clinical trials. Depending on the predominant motor symptom, MSA is classified into two clinical phenotypes: MSA with predominant cerebellar ataxia (MSA-C) and MSA with predominant parkinsonism (MSA-P). Glial cytoplasmic inclusions (GCIs) found in oligodendroglial cells, composed of α-synuclein, have been recognized as the neuropathological hallmarks of MSA [2]; however, the origin of α-synuclein deposition in GCIs remains to be understood and the exact mechanisms leading to propagation and neurodegeneration remain elusive.

The second consensus criteria by Gilman and colleagues have been widely accepted for the diagnosis of MSA [3], but the sensitivity of the criteria is only moderate, particularly in the early stages of the disorder [4]. Although the inclusion criteria include only the pons and middle cerebellar peduncle (MCP) atrophy as features of MSA-C on magnetic resonance imaging (MRI) [3], other MRI findings such as the "hot cross bun" sign and hyperintensities in MCP on T2-weighted or fluid-attenuated inversion recovery images have been described as additional features of MSA-C [5]. The "hot cross bun" sign is a cruciform hyperintensity in the pons on T2-weighted images and has been reported to be a typical feature of MSA-C [6]. MCP hyperintensities have been repeatedly reported to be useful in the diagnosis of MSA-C [6–12], and to reflect MCP myelin loss [6]. However, these MRI findings are not based on quantitative measures and may not be sufficient as objective and sensitive imaging biomarkers.

Recently, the ratio of the signal intensity of the T1-weighted and T2-weighted (T1w/T2w ratio) images has been proposed as a unique quantitative contrast, with high spatial resolution and test–retest reliability [13, 14]. Compared to other MRI measures, this method provides convenience as T1w and T2w images are standard MRI sequences that are easily acquired during routine clinical MRI. Furthermore, there is no advanced image processing required, except for the registration of both images. The ratio has been reported to be sensitive to myelin in the human cerebral cortex [15, 16]. A previous study found that the subcortical T1w/T2w ratio was associated with neurodegenerative changes in Parkinson's disease [17]. Recently, a standardization of the T1w/T2w ratio (sT1w/T2w ratio) was proposed, allowing for a meaningful comparison between subjects and scanners by creating scaled intensity values and also correcting for inhomogeneities from the receive coil sensitivity [18]. The sT1w/T2w ratio has also been shown to be increasingly sensitive for detecting disease-related changes, for example, in multiple sclerosis [19]. Therefore, applying the sT1w/T2w ratio in MCP of MSA-C patients may help detect early MSA-C-related degenerative changes (such as myelin loss), and serve as quantitative imaging biomarker of disease progression.

In this study, we sought to clarify whether the sT1w/T2w ratio can help detect MSA-C-related changes, even in early stages of the disease. For this purpose, we compared the MCP sT1w/T2w ratio between MSA-C patients and matched controls, and also between a subgroup of early-stage MSA-C patients and controls. Moreover, to clarify whether the sT1w/T2w ratio can serve as an objective marker of the degree of damage due to MSA-C-related degeneration, we investigated the correlation between the MCP sT1w/T2w ratio and clinical parameters including cerebellar ataxia scores of MSA-C patients.

Methods

Subjects

This retrospective study was approved by the Institutional Review Board of the Chiba University Graduate School of Medicine and the need for informed consent was waived. Patients with MSA-C who were seen at the Chiba University Hospital between September 2017 and January 2020 were identified from our database. The inclusion criterion was patients who qualified the criteria for clinically possible or probable MSA-C, as described in the second consensus statement by Gilman and colleagues [3], with the terms "possible" and "probable" reflecting the levels of diagnostic certainty. The exclusion criteria were as follows: (1) current or previous history of another neuropsychiatric disorder; (2) abnormal MRI due to another etiology. Based on these criteria, a total of 28 MSA-C patients (probable 23, possible 5) were included in the present study. Early-stage MSA-C (early MSA-C) was defined as disease duration ≤ 2 years; based on this definition,

MSA-C patients were divided into 2 subgroups: early MSA-C ($n = 17$) and nonearly MSA-C ($n = 11$). Twenty-eight age- and sex-matched healthy subjects who volunteered in response to local advertisement served as healthy controls. These healthy subjects had no history of neurological or psychiatric illnesses or head injury, and had a normal neurological examination.

The medical records of the MSA-C patients were reviewed for age at onset, age at the time of MRI scan, disease duration (time from onset of motor symptoms to MRI scan), the International Cooperative Ataxia Rating Scale (ICARS) scores, and the Unified Multiple System Atrophy Rating Scale (UMSARS) part 2 scores. ICARS is a scale for assessing cerebellar ataxia. UMSARS is a disease-specific scale for assessing MSA, with part 2 measuring motor impairment. In both the scales, high scores indicate high disease severity.

MRI acquisition

All MRI studies were performed using a 3-T MRI system (GE DISCOVERY MR750, GE Healthcare). The MRI parameters for T1w images were 3D-IR-SPGR; sagittal plane; TR, 8 ms; TE, 3 ms; TI, 420 ms; flip angle, 15°; FOV, 256 mm; matrix, 256 × 256; and voxel size, 1 × 1 × 1 mm. The MRI parameters for T2w were 2D-TSE; TR, 5000 ms; TE, 93 ms; FOV, 220 × 220 mm; matrix, 352 × 352; voxel size, 0.43 × 0.43 × 5 mm; and interslice gap, 1 mm.

MRI preprocessing

Before the calculation of the sT1w/T2w ratio, the T1w and T2w images were preprocessed as follows. The 3D T1w images were linearly co-registered with the 2D axial T2w images using SPM12 (version 7219) in Matlab 2014a. Brain masks were created by skull-stripping the co-registered T1w images using the Brain Extraction Tool with FSL (version 5.0.11) [20] and binarizing it with FSLmaths. Gray matter and white matter brain masks were generated using FMRIB Automatic Segmentation Tool (FSL FAST) on the co-registered T1w image [21].

T1w/T2w ratio and standardized T1w/T2w ratio calculation

Median intensity values on T1w and T2w images in both gray matter and white matter brain masks from each subject were calculated using FSLstats. In order to calculate the sT1w/T2w ratio, a scaling factor was calculated by dividing the median gray matter intensity value in the T1w images by the median gray matter intensity value in the T2w image. A scaled T2w image (sT2) was then created by multiplying the T2w image by the scaling factor. Finally, the sT1w/T2w ratio was calculated using the following equation developed by Misaki et al [18].

$$s\frac{T1w}{T2w}ratio = \frac{T1w - sT2}{T1w + sT2}$$

The sT1w/T2w ratio map in each subject was normalized into Montreal Neurological Institute 152 space [22] by the software package SPM12 in Matlab 2014a. Each image was spatially smoothed with an 8-mm full-width at half-maximum Gaussian kernel. Bilateral MCP regions of interest were set on the normalized sT1w/T2w ratio maps using a validated probabilistic 3D atlas of the cerebellar white matter structure by SPM12 in Matlab 2014a (Fig. 1) [23]. Parcellation at a 90% probability threshold was used. Atlas registration accuracy was visually verified using the check registration tool of SPM12 in Matlab 2014a. The median value of the sT1w/T2w ratio on each side of MCP was extracted considering that the sT1w/T2w ratio was not always normally distributed. The mean of median sT1w/T2w ratio values in the left and right MCP regions was used as each subject's MCP sT1w/T2w ratio value.

Visual interpretation of the MCP hyperintensities

Two board-certified neuroradiologists (H.Y. and H.M., with 14 and 12 years of experience, respectively) were blinded to the clinical data; they independently evaluated the MCP hyperintensities for each subject. When interpretations

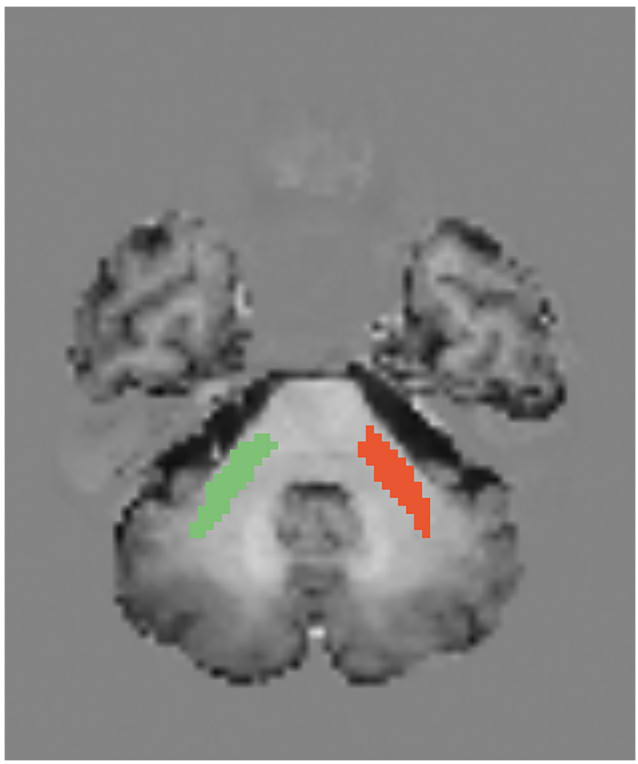

Fig. 1 Regions of interest in the bilateral middle cerebellar peduncles. Regions of interest are set in the bilateral middle cerebellar peduncles (right, green; left, red)

differed, the final result was determined by consensus of the two neuroradiologists and a board-certified neurologist (A.S., with 12 years of experience). The MCP hyperintensities were marked as absent or present. Images were defined as present for the MCP hyperintensities when high intensities relative to adjacent white matter in the brainstem and cerebellum were observed at least on one side of the MCP.

Statistical analysis

All statistical analyses, except for receiver operating characteristic (ROC) curve analyses, were performed using the SPSS software (version 25.0) (SPSS Inc. IBM). ROC curve analyses were performed using JMP pro 14.2.0 (SAS Institute). Demographic data of the MSA-C patients and controls were compared using the χ^2 test for sex and Mann-Whitney *U* test for age at the time of MRI scan. Demographic data of the early and nonearly MSA-C patients and controls were compared using the χ^2 test for sex, Kruskal–Wallis test for age at the time of MRI scan, Student's *t* test for age at onset and the ICARS score, and Mann–Whitney *U* test for disease duration and the UMSARS part 2 score. MCP sT1w/T2w ratio values were compared between controls and MSA-C patients using Student's *t* test. MCP sT1w/T2w ratio values were compared among controls and early and nonearly MSA-C patients using univariate one-way analysis of variance (Welch statistics for *p* values). Games–Howell test was used as a post hoc test for pairwise comparisons. The ability of MCP sT1w/T2w ratio values to discriminate MSA-C and early MSA-C patients from controls was assessed using ROC curve analyses. The optimal cutoff point was determined using the Youden method [24]. The relationship between MCP sT1w/T2w ratio values and normally distributed variables including age at the time of MRI scan and age at motor symptom onset was evaluated using Pearson correlation analysis. However, Spearman correlation analysis was used to evaluate the relationship between MCP sT1w/T2w ratio values and nonnormally distributed variables including sex, disease duration, and UMSARS and ICARS scores. $p < 0.05$ was considered statistically significant. The interrater agreement for visual interpretation of MCP hyperintensities was tested using Cohen's κ statistics.

Results

Demographic and clinical data of patients with MSA-C and controls are summarized in Table 1. There were no significant differences between MSA-C patients and controls in gender and age at the time of the MRI scan. Demographic and clinical data of early and nonearly MSA-C patients and controls are summarized in Table 2. Disease duration was significantly longer in nonearly MSA-C patients than in early MSA-C patients ($p < 0.001$).

MCP sT1w/T2w ratio value for overall MSA-C

The MCP sT1w/T2w ratio values for all MSA-C patients were significantly lower than those for controls (-0.05 ± 0.09 vs. 0.18 ± 0.04; $p < 0.001$) (Fig. 2). The area under the curve (AUC), which was used to differentiate overall MSA-C patients from controls, was 0.994 [95% confidence interval (CI), 0.9486–0.9992], with a sensitivity of 0.964 and specificity of 1.0 (Fig. 3).

There was no significant correlation between the MCP sT1w/T2w ratio value and clinical variables, including gender, age at the time of the MRI scan, disease duration, and UMSARS and ICARS scores in overall MSA-C patients (Fig. 4).

MCP sT1w/T2w ratio value for early MSA-C

The MCP sT1w/T2w ratio values for early (-0.05 ± 0.10) and nonearly (-0.05 ± 0.05) MSA-C patients were markedly lower than that for controls (0.18 ± 0.04; $p < 0.001$) (Fig. 2). There

Table 1 Demographic and clinical data of patients with MSA-C and healthy controls

Group	MSA-C	Control	*p* value
Total no.	28	28	
Sex (male/female)[a]	19/9	16/12	0.408
Age at MRI, years (median (range))[b]	63.0 (46–75)	65.4 (42–75)	0.225
Age at onset, years (mean ± SD)	59.9 ± 8.5	NA	NA
Disease duration, years (median (range))	1.6 (0.7–5.3)	NA	NA
UMSARS part 2 score (median (range))	11.0 (6–26)	NA	NA
ICARS score (median (range))	28.0 (14–63)	NA	NA

MRI, magnetic resonance imaging; *SD*, standard deviation; *NA*, not applicable; *UMSARS*, Unified Multiple System Atrophy Rating Scale; *ICARS*, International Cooperative Ataxia Rating Scale

[a] χ^2 test

[b] Mann-Whitney *U* test

Table 2 Demographic and clinical data of patients with early MSA-C, nonearly MSA-C, and healthy controls

Group	Early MSA-C	Nonearly MSA-C	Control	*p* value
Total no.	17	11	28	
Sex (male/female)[a]	10/7	9/2	16/12	0.334
Age at MRI, years (median (range))[b]	63.0 (46–72)	59.0 (48–75)	65.4 (42–75)	0.448
Age at onset, years (mean ± SD)[c]	61.2 ± 7.9	57.8 ± 9.2	NA	0.314
Disease duration, years (median (range))[d]	1.3 (0.7–2.0)	2.6 (2.1–5.3)	NA	< 0.001
UMSARS part 2 score (median (range))[d]	11.0 (7–19)	10.0 (6–26)	NA	0.817
ICARS score (mean ± SD)[c]	29.4 ± 8.0	31.0 ± 16.9	NA	0.775

Early MSA-C is defined by disease duration within 2 years

MRI, magnetic resonance imaging; *SD*, standard deviation; *NA*, not applicable; *UMSARS*, Unified Multiple System Atrophy Rating Scale; *ICARS*, International Cooperative Ataxia Rating Scale

[a] χ^2 test

[b] Kruskal–Wallis test

[c] Student's *t* test

[d] Mann-Whitney *U* test

was no significant difference between early and nonearly MSA-C patients in the MCP sT1w/T2w ratio value. The AUC for differentiating early MSA-C patients from controls was 0.990 (95% CI, 0.9170–0.9988), with a sensitivity of 0.941 and a specificity of 1.0 (Fig. 3).

In early MSA-C patients, the MCP sT1w/T2w ratio value was inversely correlated with the ICARS score ($r = -0.530$; $p = 0.029$) (Fig. 4) even after controlling for age at the time of the MRI scan ($r = -0.507$; $p = 0.045$). There were no significant correlations between the MCP sT1w/T2w ratio values and other clinical variables.

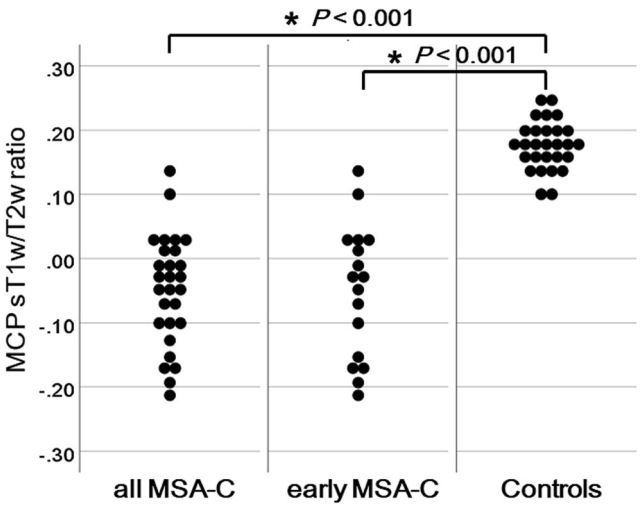

Fig. 2 Group comparison of the standardized T1-weighted/T2-weighted (sT1w/T2w) ratio in the middle cerebellar peduncle in cerebellar subtype multiple system atrophy (MSA-C) and early MSA-C patients and controls. The middle cerebellar peduncle sT1w/T2w ratio (MCP sT1w/T2w ratio) was significantly lower in MSA-C and early MSA-C than in controls (*$p < 0.001$)

Visual evaluation of MCP hyperintensities

The κ value for interrater variability between the two examiners was 0.782 for visual evaluation of the MCP hyperintensities. The MCP hyperintensities were found in 25 of 28 all MSA-C patients (89.3%), 14 of 17 early MSA-C patients (82.4%), and none of 28 healthy controls (0%).

Discussion

Our results showed that the MSA-C patients exhibited a significantly lower MCP sT1w/T2w ratio than the normal controls. This finding was also confirmed in MSA-C patients in the early disease stage (≤ 2 years of disease). The MCP sT1w/T2w ratio had high sensitivity and specificity to discriminate MSA-C patients and controls, a finding that also applied to very early MSA-C patients. These findings suggest that the MCP sT1w/T2w ratio can detect early MSA-C-related changes. Moreover, the MCP sT1w/T2w ratio value was inversely correlated with cerebellar ataxia scores in very early MSA-C patients, suggesting that the MCP sT1w/T2w ratio value might serve as an objective marker for damage of the olivopontocerebellar system.

The sT1w/T2w ratio can detect early MSA-C-related changes in the MCP. In our study, early MSA-C patients had a significantly lower MCP sT1w/T2w ratio compared to controls. Moreover, the MCP sT1w/T2w ratio value showed a high discriminatory capacity between early MSA-C and controls. The core feature of MSA pathology is the widespread presence of GCIs, and the density of GCIs that contain α-synuclein significantly correlates with disease progression [1]. The pontocerebellar fibers in MCP have been shown to be one of the regions where GCI

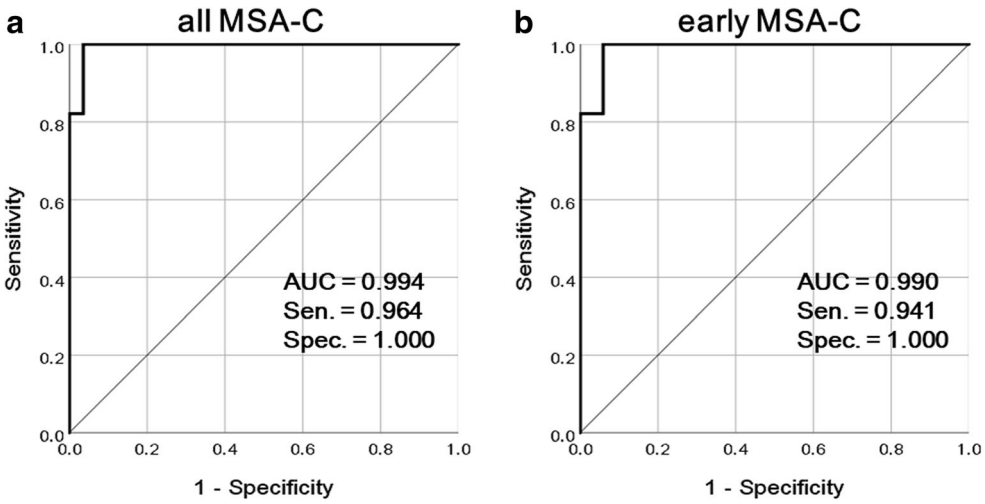

Fig. 3 Receiver operating characteristics (ROC) curve analysis of the middle cerebellar peduncle standardized T1-weighted/T2-weighted (sT1w/T2w) ratio showing the area under the curve (AUC), sensitivity (Sen), and specificity (Spec). **a** and **b** are the ROC curves distinguishing cerebellar subtype multiple system atrophy (MSA-C) (**a**) and early MSA-C (**b**) patients from controls

pathology progresses in the earliest phase of the disease in MSA-C patients, in addition to the olivocerebellar fibers in the medulla, the inferior cerebellar peduncle of the medulla, and the cerebellar subcortical white matter [25]. A recent study using diffusion tensor imaging also showed that white matter changes predominantly affecting the infratentorial white matter including MCP were observed in early MSA-C patients (≤ 2.5 years of disease) [26]. The regional severity of GCI pathology correlated with the severity of myelin loss [25]. Recently, myelin content was shown to be associated with both T1w and T2w intensity values, but in opposite directions [13], and that the T1w/T2w ratio has been shown to be associated with myelin in the human cerebral cortex [15, 16]. Myelin loss can be the main biological substrate for decreased sT1w/T2w ratio, with decrease in lipids contributing to a decreased T1w signal and increase in water content and the ratio of free to myelin-bound water contributing to an increased T2w signal [27–29]. Therefore, it is reasonable to suggest that application of the sT1w/T2w ratio can help more sensitively detect myelin loss in MCP as a decreased sT1w/T2w ratio compared with the method of qualitative evaluation of hyperintensities on T2w images only.

Previous studies have shown that MCP hyperintensities, which are thought to reflect myelin loss in MCP [6], have a relatively high sensitivity of 68.3–87% depending on disease duration [11, 12]. The frequency of the MCP hyperintensities in MSA-C patients of our study is comparable with that of previous reports. In the current study, MCP sT1w/T2w ratio showed higher sensitivity than visual evaluation of the MCP hyperintensities for diagnosis of MSA-C. An advantage of applying the sT1w/T2w ratio is that the MCP sT1w/T2w ratio might more sensitively help detect degenerative changes in MCP of MSA-C patients in early disease stage compared with visual evaluation of MCP hyperintensities.

Another advantage of the sT1w/T2w ratio over visual evaluation of MCP hyperintensities is that the former can be quantitatively evaluated. An objective biomarker of disease progression is of paramount importance for evaluating the efficacy of disease-modifying therapies in clinical trials, and the MCP sT1w/T2w ratio may be an objective marker of damage to the olivopontocerebellar system in

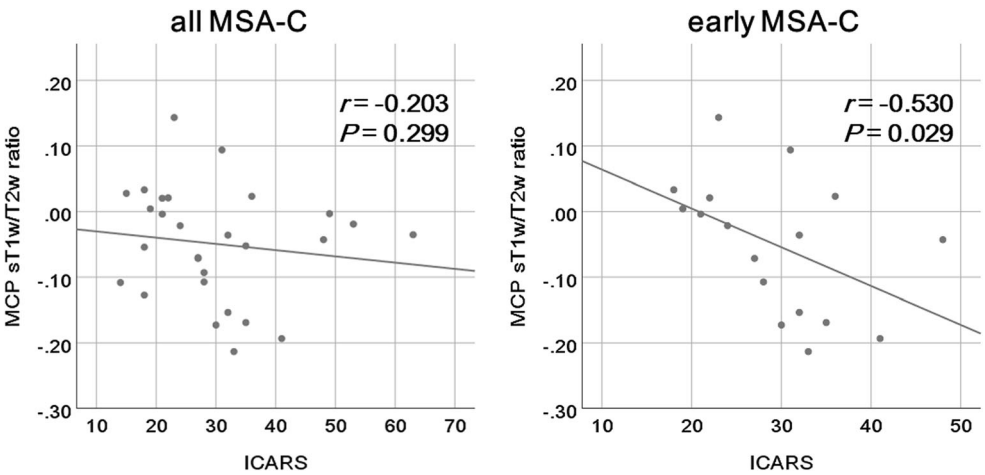

Fig. 4 Correlations between the middle cerebellar peduncle standardized T1-weighted/T2-weighted (sT1w/T2w) ratio and the International Cooperative Ataxia Rating Scale (ICARS) score in cerebellar subtype multiple system atrophy (MSA-C) and early MSA-C patients. The sT1w/T2w ratio in the middle cerebellar peduncle (MCP sT1w/T2w ratio) was inversely correlated with ICARS in patients with early MSA-C

MSA-C patients. In our study, the MCP sT1w/T2w ratio value was inversely correlated with the ICARS scores in early MSA-C patients. Previous studies have also shown that the MCP hyperintensities correlate with cerebellar symptoms [10, 11]. However, in those studies, cerebellar symptoms were not assessed using validated scales such as ICARS or the Scale for the Assessment and Rating of Ataxia (SARA). A possible explanation for the lack of correlation between the MCP sT1w/T2w ratio value and ICARS in all MSA-C patients in the current study might be that confounding factors other than cerebellar symptoms, such as parkinsonism, tremor/myoclonus, camptocormia, Pisa syndrome, contractures, and disuse, affected the ICARS score. For example, parkinsonism has been shown to develop as a secondary motor symptom in MSA-C patients with long disease duration [30, 31]. In addition, ascribing motor slowness, unsteadiness, or dysarthria to cerebellar dysfunction or parkinsonism origin is frequently difficult in clinical practice. Indeed, parkinsonism has been shown to contaminate ICARS score ratings in MSA patients [32]. It has been reported that progressive striatal degeneration may be the underlying pathologic substrate of Pisa syndrome [33]. Tremor/myoclonus, camptocormia, and contractures are more common in MSA-P than in MSA-C patients [34, 35]. Pathological involvement of the striatonigral system, which is a main substrate of MSA-P, has been shown to be correlated with disease duration in MSA [36]. Therefore, these factors are expected to more frequently affect ICARS scores in late MSA-C than early MSA-C patients with short disease duration.

The lack of correlation between the UMSARS part 2 score and the MCP sT1w/T2w ratio value might be due to UMSARS part 2 being constructed to measure not only cerebellar ataxia but also parkinsonism [37]. Age was reported to affect T1w/T2w ratio [38]; however, no significant correlation between age and the MCP sT1w/T2w ratio was found in this study. This may be because the MSA-C cohort included in this study was relatively small and the effect of the disease on the MCP sT1w/T2w ratio was larger than that of age.

One strength of this study was that more than half of MSA-C patients were very early-stage MSA-C patients (≤ 2 years of disease); thus, allowing us to investigate if the MCP sT1w/T2w ratio is a sensitive marker for early disease stages of MSA-C. There are several limitations in this study such as the lack of comparison using other quantitative methods, including diffusion-weighted imaging and volumetric analysis of MCP. To clarify which methods are better for detecting MSA-C-related early changes in the MCP, future studies are needed to compare their diagnostic performance directly. Second, MSA-C patients were clinically diagnosed without postmortem confirmation and the possibility of misdiagnosis in some of these patients could not be excluded. Finally, this study was retrospective and did not include a large cohort of MSA-C patients. To confirm the usefulness of MPC sT1w/T2w ratio for diagnosing the early disease stage and as an objective marker of damage to the olivopontocerebellar system in MSA-C patients, further longitudinal studies including large MSA-C cohorts are needed.

In summary, the sT1w/T2w ratio can detect MSA-C-related changes in the MCP, even in early disease stages. The MCP sT1w/T2w ratio may be used as a novel, objective marker for damage of the olivopontocerebellar system in MSA-C.

Funding MRI of healthy subjects was funded by Nihon Medi-physics, Co. Ltd., Japan.

Compliance with ethical standards

Guarantor The scientific guarantor of this publication is Prof. Satoshi Kuwabara.

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 waived by the Institutional Review Board.

Ethical approval Institutional Review Board approval was obtained.

Methodology
- prospective
- case-control study/observational
- performed at one institution

References

1. Stefanova N, Bücke P, Duerr S, Wenning GK (2009) Multiple system atrophy: an update. Lancet Neurol 8:1172–1178
2. Trojanowski JQ, Revesz T, Neuropathology Working Group on MSA (2007) Proposed neuropathological criteria for the post mortem diagnosis of multiple system atrophy. Neuropathol Appl Neurobiol 33:615–620
3. Gilman S, Wenning GK, Low PA et al (2008) Second consensus statement on the diagnosis of multiple system atrophy. Neurology 71:670–676
4. Osaki Y, Ben-Shlomo Y, Lees AJ, Wenning GK, Quinn NP (2009) A validation exercise on the new consensus criteria for multiple system atrophy. Mov Disord 24:2272–2276
5. Brooks DJ, Seppi K, Neuroimaging Working Group on MSA (2009) Proposed neuroimaging criteria for the diagnosis of multiple system atrophy. Mov Disord 24:949–964
6. Savoiardo M, Strada L, Girotti F et al (1990) Olivopontocerebellar atrophy: MR diagnosis and relationship to multisystem atrophy. Radiology 174:693–696

7. Schrag A, Kingsley D, Phatouros C et al (1998) Clinical usefulness of magnetic resonance imaging in multiple system atrophy. J Neurol Neurosurg Psychiatry 65:65–71
8. Naka H, Ohshita T, Murata Y, Imon Y, Mimori Y, Nakamura S (2002) Characteristic MRI findings in multiple system atrophy: comparison of the three subtypes. Neuroradiology 44:204–209
9. Bhattacharya K, Saadia D, Eisenkraft B et al (2002) Brain magnetic resonance imaging in multiple-system atrophy and Parkinson disease: a diagnostic algorithm. Arch Neurol 59:835–842
10. Lee EA, Cho HI, Kim SS, Lee WY (2004) Comparison of magnetic resonance imaging in subtypes of multiple system atrophy. Parkinsonism Relat Disord 10:363–368
11. Bürk K, Bühring U, Schulz JB, Zühlke C, Hellenbroich Y, Dichgans J (2005) Clinical and magnetic resonance imaging characteristics of sporadic cerebellar ataxia. Arch Neurol 62:981–985
12. Kim M, Ahn JH, Cho Y, Kim JS, Youn J, Cho JW (2019) Differential value of brain magnetic resonance imaging in multiple system atrophy cerebellar phenotype and spinocerebellar ataxias. Sci Rep 9:17329
13. Glasser MF, Van Essen DC (2011) Mapping human cortical areas in vivo based on myelin content as revealed by T1- and T2- weighted MRI. J Neurosci 31:11597–11616
14. Arshad M, Stanley JA, Raz N (2017) Test-retest reliability and concurrent validity of in vivo myelin content indices: myelin water fraction and calibrated T_1w/T_2w image ratio. Hum Brain Mapp 38: 1780–1790
15. Glasser MF, Goyal MS, Preuss TM, Raichle ME, Van Essen DC (2014) Trends and properties of human cerebral cortex: correlations with cortical myelin content. Neuroimage 93:165–175
16. Nakamura K, Chen JT, Ontaneda D, Fox RJ, Trapp BD (2017) T1-/T2-weighted ratio differs in demyelinated cortex in multiple sclerosis. Ann Neurol 82:635–639
17. Du G, Lewis MM, Sica C, Kong L, Huang X (2019) Magnetic resonance T1w/T2w ratio: a parsimonious marker for Parkinson disease. Ann Neurol 85:96–104
18. Misaki M, Savitz J, Zotev V et al (2015) Contrast enhancement by combining T1- and T2-weighted structural brain MR images. Magn Reason Med 74:1609–1620
19. Cooper G, Finke C, Chien C et al (2019) Standardization of T1w/T2w ratio improves detection of tissue damage in multiple sclerosis. Front Neurol 263:1495–1502
20. Smith SM, Jenkinson M, Woolrich MW et al (2004) Advances in functional and structural MR image analysis and implementation as FSL. Neuroimage 23:S208–S219
21. Zhang Y, Brady M, Smith S (2001) Segmentation of brain MR images through a hidden Markov random field model and the expectation-maximization algorithm. IEEE Trans Med Imaging 20:45–57
22. Fonov V, Evans AC, Botteron K et al (2011) Unbiased average age-appropriate atlases for pediatric studies. Neuroimage 54:313–327
23. van Baarsen KM, Kleinnijenhuis M, Jbabdi S, Sotiropoulos SN, Grotenhuis JA, van Cappellen van Walsum AM (2016) A probabilistic atlas of the cerebellar white matter. Neuroimage 124:724–732
24. Fluss R, Faraggi D, Reiser B (2005) Estimation of the Youden index and its associated cutoff point. Biom J 47:458–472
25. Brettschneider J, Irwin DJ, Boluda S et al (2017) Progression of alpha-synuclein pathology in multiple system atrophy of the cerebellar type. Neuropathol Appl Neurobiol 43:315–329
26. Dash SK, Stezin A, Takalkar T, George L, Kamble NL, Netravathi M et al (2019) Abnormalities of white and gray matter in early multiple system atrophy: comparison of parkinsonian and cerebellar variants. Eur Radiol 29:716–724
27. Koenig SH (1991) Cholesterol of myelin is the determinant of gray-white contrast in MRI of brain. Magn Reson Med 20:285–291
28. Miot-Noirault E, Barantin L, Akoka S, Le Pape A (1997) T2 relaxation time as a marker of brain myelination: experimental MR study in two neonatal animal models. J Neurosci Methods 72:5–14
29. Barkovich AJ (2000) Concepts of myelin and myelination in neuroradiology. AJNR Am J Neuroradiol 21:1099–1109
30. Yabe I, Soma H, Takei A, Fujiki N, Yanagihara T, Sasaki H (2006) MSA-C is the predominant clinical phenotype of MSA in Japan: analysis of 142 patients with probable MSA. J Neurol Sci 249:115–121
31. Tada M, Onodera O, Tada M et al (2007) Early development of autonomic dysfunction may predict poor prognosis in patients with multiple system atrophy. Arch Neurol 64:256–260
32. Tison F, Yekhlef F, Balestre E et al (2002) Application of the International Cooperative Ataxia Scale Rating in multiple system atrophy. Mov Disord 17:1248–1254
33. Hozumi I, Piao YS, Inuzuka T et al (2004) Marked asymmetry of putaminal pathology in an MSA-P patient with Pisa syndrome. Mov Disord 19:470–472
34. Kaindlstorfer C, Granata R, Wenning GK (2013) Tremor in multiple system atrophy – a review. Tremor Other Hyperkinet Mov (N Y) 3:tre-03-165-4252-1
35. Miki Y, Foti SC, Asi YT et al (2019) Improving diagnostic accuracy of multiple system atrophy: a clinicopathological study. Brain 142:2813–2827
36. Ozawa T, Paviour D, Quinn NP et al (2004) The spectrum of pathological involvement of the striatonigral and olivopontocerebellar systems in multiple system atrophy: clinicopathological correlations. Brain 127:2657–2671
37. Wenning GK, Tison F, Seppi K et al (2004) Development and validation of the Unified Multiple System Atrophy Rating Scale (UMSARS). Mov Disord 19:1391–1402
38. Operto G, Molinuevo JL, Cacciaglia R et al (2019) Interactive effect of age and APOE-ε4 allele load on white matter myelin content in cognitively normal middle-aged subjects. Neuroimage Clin 24: 101983