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Letter to the Editor

Sleep Apnea in Multiple System Atrophy of Cerebellar Type: A 3.0 T MRS/Volumetry Pilot Study

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In a previous study, we demonstrated that the ratio of glutamate to creatine (Glu/Cr) is reduced in the pons of multiple system atrophy of cerebellar type (MSA-C) patients compared to the control subjects [1]. Given the presence of respiratory centers in the brainstem [2], we hypothesized that the Glu/Cr of the pons could be a biomarker of respiratory dysfunction, such as sleep apnea, in individuals with MSA-C. Thus, we retrospectively analyzed the clinical data of eight MSA-C patients [64.8 ± 6.5 (mean $\pm$ SD)] investigated with polysomnography (PSG) [3], to correlate the severity of sleep apnea with brainstem metabolites as measured by magnetic resonance spectroscopy (^{1}H–MRS). We selected the apnea hypoxia index (AHI) to indicate the severity of sleep apnea as described in a previous study [4]. Because atrophy of the brainstem is known to correlate with disease progression [5], we also performed volumetric analysis of both the pons and medulla to examine the relationship between their volume and respiratory dysfunction severity. These data were compared with 11 age-matched control subjects (66.4 ± 6.7). This study was approved by the Ethics Committee of Niigata University.

MRI/^{1}H–MRS was performed on a 3.0 T system (Signa LX, General Electric, Waukesha, WI). T1-weighted images were used for volumetric analysis. The pons was defined manually using ITK-SNAP [6]. The pons and cerebellum were separated by transecting the cerebellar peduncles along the plane of their entrance into the pons [6]. Brainstem metabolites of the previous ^{1}H–MRS dataset of the eight MSA-C patients were reanalyzed for this study [1]. Statistical analysis was performed using *SPSS* 15.0 statistical software (SPSS, Chicago, IL). Metabolite ratios of the patients were compared to those of the control subjects using the Student's unpaired *t*-test or Mann–Whitney rank sum test where appropriate. Associations between AHI and MRI/^{1}H–MRS values were tested for significance using the Spearman rank correlation coefficient. The significance level was defined as $p < 0.05$. The results of correlations between AHI and MRI/^{1}H–MRS values are summarized in Table 1. In brief, the volume of the pons in MSA-C patients was significantly reduced compared to the control subjects ($p < 0.001$), while there was no correlation between the volume of the pons and AHI. Glu/Cr in the pons was significantly decreased ($p < 0.001$) and negatively correlated with AHI in MSA-C patients ($r = -0.857$, $p < 0.05$) (See Fig. 1.).

Although Glu/Cr, measured by ^{1}H–MRS in a voxel of interest (VOI), is known to constitute a general marker for neuronal or synaptic health [7], it can also be associated with brain excitability [8]. Thus, we assume that metabolites measured by VOI in the pons may reflect its brain function. Respiration is controlled by respiratory centers in the brainstem [2,9]; the pneumotaxic center in the pons in addition to the ventral and dorsal respiratory groups in the medulla are considered important components of those centers. In those centers, neurotransmitters, such as glutamate and gamma-aminobutyric acid, are known to work on the respiratory centers [2]. Based on the correlation between Glu/Cr in the pons and AHI, we considered that the reduction of Glu/Cr in the pons reflects the loss and/or dysfunction of excitatory neurons in those regions in MSA-C patients. The concentrations of other metabolites (such as *N*-acetylaspartate, choline, and *myo*-inositol) were also significantly changed in MSA-C patients compared to the control subjects. However, the levels of these metabolites did not show any correlation with AHI despite the significant change in their concentrations (Table 1), thus strengthening the importance of Glu/Cr in the pons as a biomarker of respiratory dysfunction. The volume of the pons was also significantly decreased compared to the control subjects; however, there was no correlation between the volume of the pons and AHI. This shows that MRS is a valuable tool for estimating brain function that cannot be examined by structural assessment of the brain. The power of neurochemical profiling by ^{1}H–MRS in neurological disorders was previously described [10].

Volumetric assessments showed that the size of the medulla in MSA-C patients is not significantly different from that in the control subjects. This suggests that in MSA-C patients, pathological changes in the pons are more relevant to the assessment of respiratory dysfunction compared to those in the medulla. This is consistent with the observation that there were no significant changes in Glu/Cr in the medulla compared to the control subjects. Given that pons has more evident changes than the medulla in MSA-C patients, this could explain the lack of correlation between Glu/Cr in the medulla and AHI. Nevertheless, it should be noted that the volume difference between the pons and medulla might also affect the sensitivity of ^{1}H–MRS measurements, resulting in a more sensitive measurement of respiratory dysfunction biomarkers in the pons than in the medulla, despite the presence of respiratory centers in the medulla [9].

This study has a few limitations. First, the number of patients with MSA-C was small because of the exploratory nature of the study. In future studies, more subjects are required to confirm the association between Glu/Cr and AHI. Second, in terms of statistics, all metabolites were measured in ^{1}H–MRS from a single spectrum, which resulted in an eventual correlation between the measured and quantified signals. Thus, the *t*-tests or Mann–Whitney rank sum test should ideally be employed as post-test, after an analysis of variance or covariance reveals significant results. Unfortunately, we could not perform them because of the small number of samples. Nevertheless, we believe that this letter contains an important finding: although morphometric MRI cannot

Table 1
Clinical profiles of MSA-C patients and control subjects.

Clinical profiles of healthy control subjects and MSA-C patients			Control vs MSA-C	Correlations with AHI	
Clinical Parameters	Control	MSA-C patients	*p* value	*r* value	*p* value
Number	11	8			
Male: Female	5: 6	4: 4			
Age	64.8 (6.5)	66.4 (6.7) n = 8			
Disease duration	–	3.13 (1.8) *n* = 8		0.415	0.307
UMSARS	–	35.3 (20.9) *n* = 8		0.323	0.435
AHI (/h)	–	41.0 (24.2) *n* = 8			
Pons volume (cm³)	12.94 (1.71) n = 11	7.54 (2.19) n = 8	< **0.001**	0.286	0.493
Medulla volume (cm³)	4.31 (0.48) n = 11	3.94 (0.43) n = 8	0.100	0.190	0.651
¹H–MRS					
tNAA/Cr (pons)	2.16 (0.24) n = 11	1.38 (0.18) n = 8	< **0.001**	-0.452	0.260
tCho/Cr (pons)	0.62 (0.08) n = 11	0.41 (0.06) n = 8	< **0.001**	0.095	0.823
MI/Cr (pons)	1.02 (0.11) n = 11	1.48 (0.16) n = 8	< **0.001**	0.500	0.207
Glu/Cr (pons)	1.08 (0.36) n = 11	0.73 (0.22) n = 7	**0.018**	-0.857	**0.014**
Glx/Cr (pons)	1.25 (0.49) n = 11	1.14 (0.21) n = 7	0.507	-0.357	0.432
tNAA/Cr (mo)	1.44 (0.18) n = 11	1.36 (0.14) n = 8	0.310	-0.048	0.911
tCho/Cr (mo)	0.48 (0.05) n = 11	0.40 (0.03) n = 8	< **0.001**	0.500	0.207
MI/Cr (mo)	1.26 (0.11) n = 11	1.58 (0.22) n = 8	< **0.001**	0.405	0.320
Glu/Cr (mo)	0.97 (0.24) *n* = 11	0.93 (0.22) *n* = 7	0.770	-0.214	0.645
Glx/Cr (mo)	1.43 (0.29) *n* = 11	1.42 (0.19) *n* = 8	0.877	0.310	0.456

AHI, apnea hypoxia index; tNAA, total *N*-acethyl-aspartate; tCho, total choline; Cr, creatine; MI, *myo*-inositol; Glu, glutamate; Gln, glutamine; Glx, sum of Glu and Gln; mo, medulla oblongata.

explain a pathology-associated loss of function, the neurochemical profiling by ¹H–MRS provides measurable variables that correlate with the measured dysfunction.

There is no doubt that understanding the mechanism of respiratory dysfunction is important in identifying therapeutic strategies for MSA-C. We consider Glu/Cr measurement by ¹H–MRS to be an invaluable tool for understanding *in vivo* brain function in a non-invasive manner.

Conflict of interest

None.
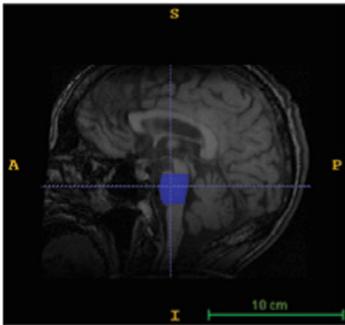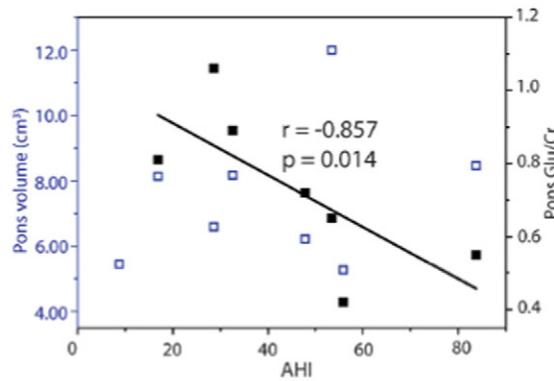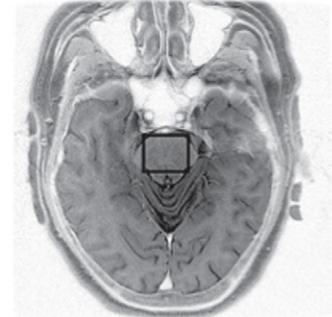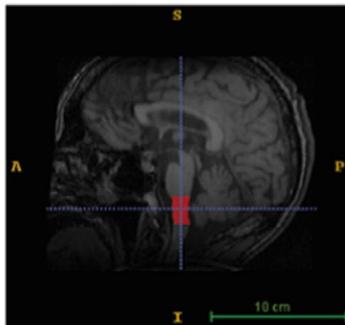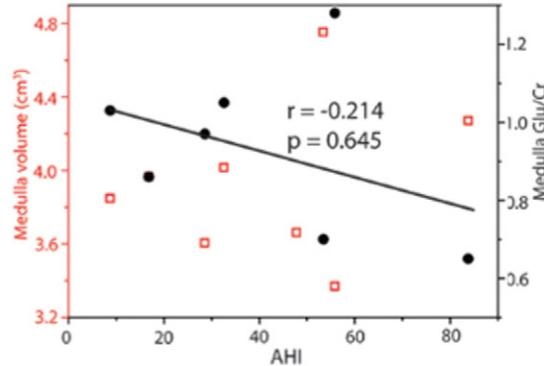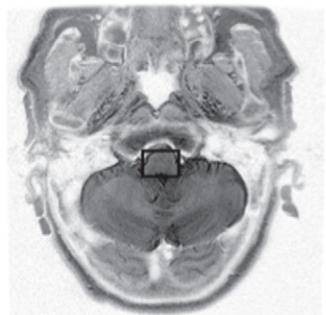
Fig. 1. Localizations of typical volumetry/¹H–MRS and scatterplots of AHI. Localizations of volumetry for pons (A) and medulla (D) as well as localizations of ¹H–MRS for pons (C) and medulla (F) are shown. The scatterplot (B) of AHI, pons volume (left y-axis, empty squares), and Glu/Cr of pons (right Y-axis, filled squares) show a negative linear correlation between AHI and Glu/Cr of pons ($r = -0.857$, $p = 0.014$). The scatterplot (E) of AHI, medulla volume (left y-axis, empty squares), and Glu/Cr of pons (right Y-axis, filled circles) did not show a negative linear correlation between AHI and Glu/Cr of medulla ($r = -0.214$, $p = 0.645$).

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